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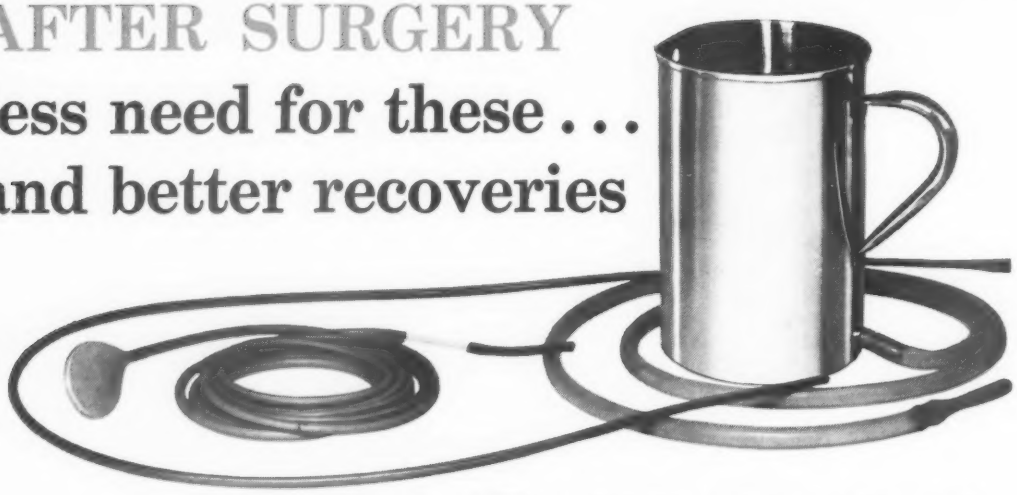

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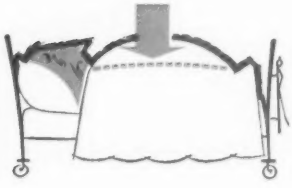

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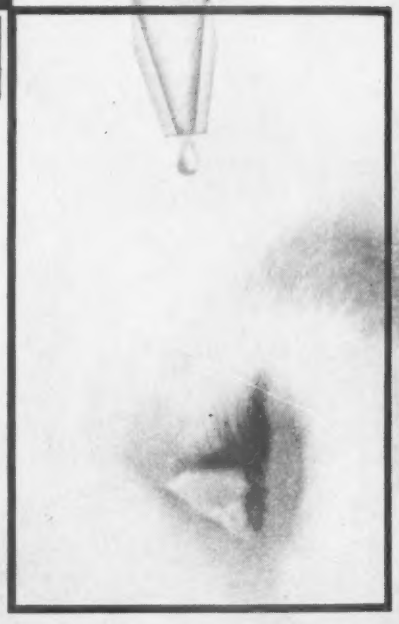

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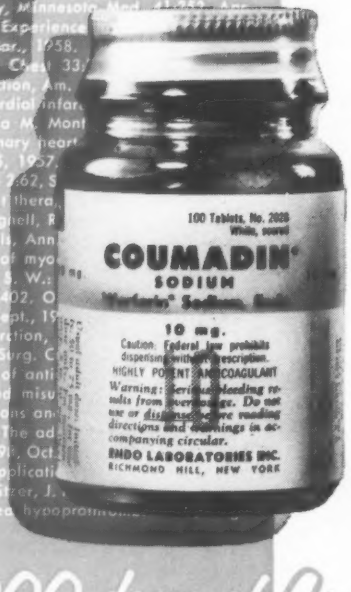

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SUPPLIED: ***Oral***—scored tablets, 2 mg., 5 mg., 7½ mg., 10 mg., 25 mg. ***Parenteral***—single injection units, consisting of one vial, 75 mg., and one 3-cc. ampul Water for Injection.

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NOW–for more comprehensive control of

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ROBAXIN® WITH ASPIRIN

ROBAXISAL, a new dual-acting muscle relaxant-analgesic, effectively treats both skeletal muscle spasm and severe pain due to or associated with the spasm. Each Tablet contains:

- A relaxant component — Robaxin* — widely recognized for its prompt, long-lasting relief of painful skeletal muscle spasm, with unusual freedom from undesired side effects. . . . . 400 mg.

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- An analgesic component—aspirin—whose pain-relieving effect is markedly enhanced by Robaxin, and which has added value as an anti-inflammatory and anti-rheumatic agent. . . . (5 gr.) 325 mg.

INDICATIONS: ROBAXISAL is indicated when analgesic as well as relaxant action is desired in the treatment of skeletal muscle spasm and severe concurrent pain. Typical conditions are disorders of the back, whiplash and other traumatic injuries, myositis, and pain and spasm associated with arthritis.

SUPPLY: ROBAXISAL Tablets (pink-and-white, laminated) in bottles of 100 and 500.
Also available: ROBAXIN Injectable, 1.0 Gm. in 10-cc ampul. ROBAXIN Tablets, 0.5 Gm. (white, scored) in bottles of 50 and 500.

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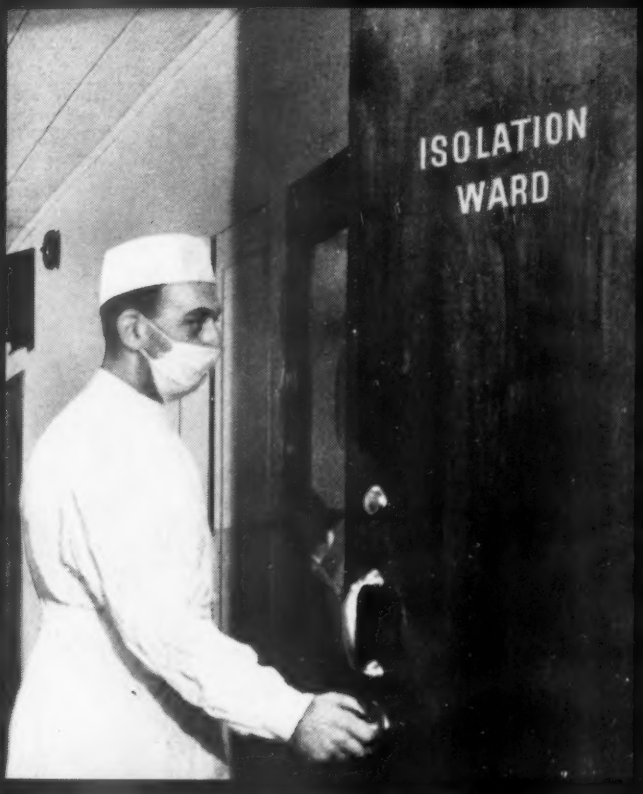

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REFERENCES 1. Glas, W. W., and Britt, E. M.: Proceedings of the Detroit Symposium on Antibacterial Therapy (Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959), p. 7. 2. Mann P. H.: Antibiotics & Chemotherapy 10:93, 1960. 3. Christenson, P. J., and Tracy, C. H.: Current Therapeutic Research 2:22, 1960. 4. Investigators' reports to the Medical Department, Eaton Laboratories. 5. Leming, B. H., Jr.: Proceedings of the Detroit Symposium on Antibacterial Therapy, 1959, p. 19. 6. Prigot, A.; Felix, A. J., and Mullins, S.: Ibid., p. 85. 7. Lysaught, J. N., and Cleaver, W.: Ibid., p. 63.

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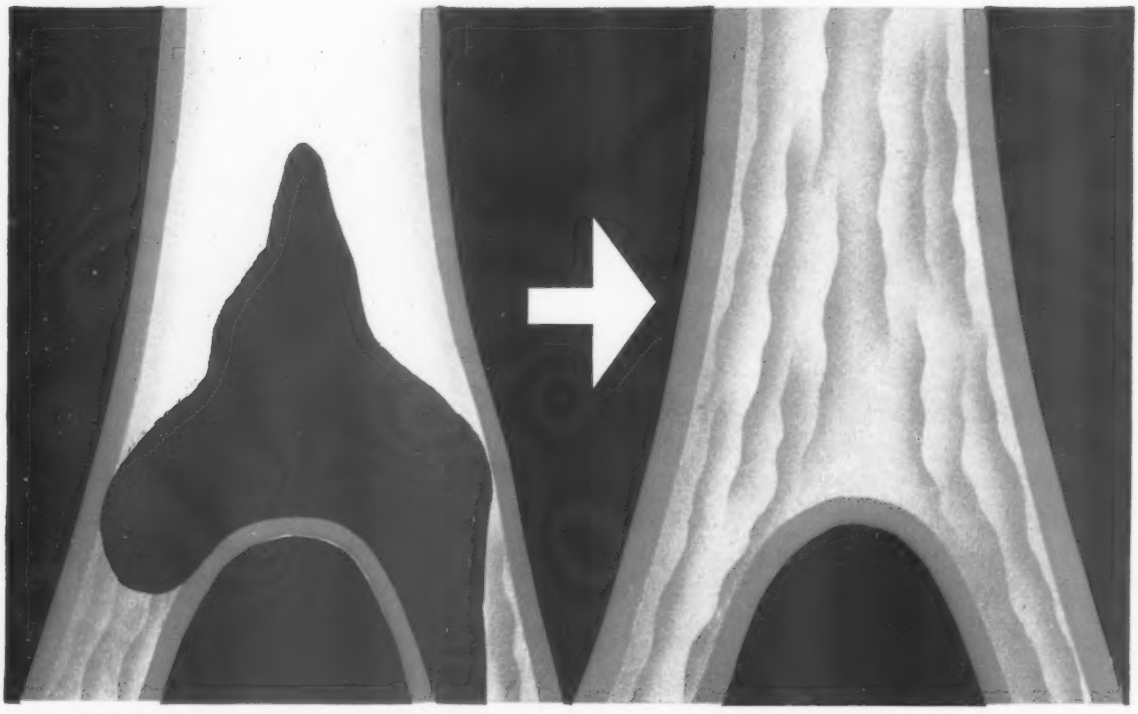

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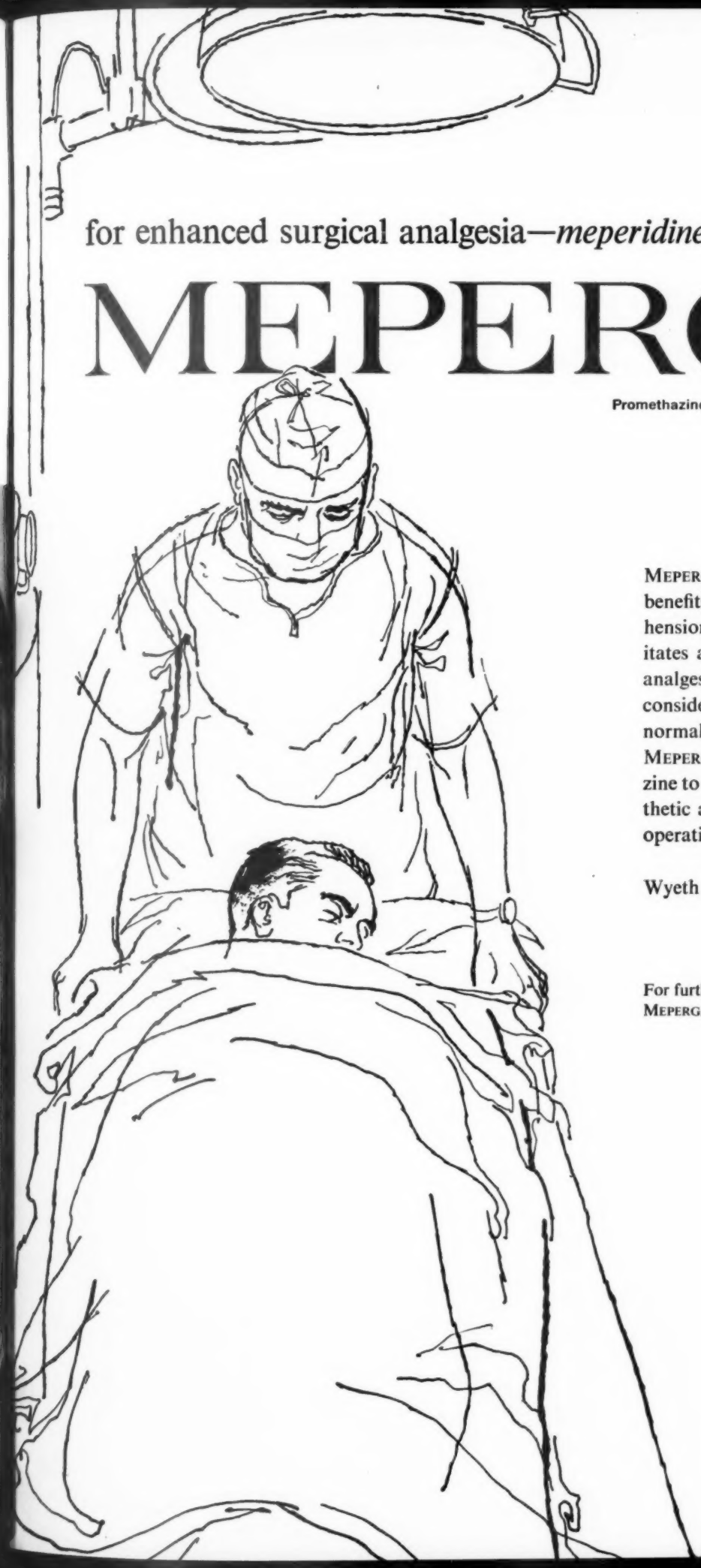

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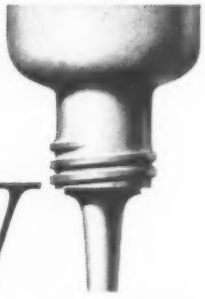

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Dosage: First day, 2 cc. (250 mg.) for each 20 lbs. body weight; thereafter, 1 cc. (125 mg.) for each 20 lbs. Should be given once a day immediately after a meal.

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Northern California Society

The 137th meeting of the Northern California Society of Hospital Pharmacists was held at the Fairmont Hospital in San Leandro on April 12.

The speaker for the evening was Dr. Malcolm A. Sowers, a psychiatrist and Clinical Instructor in Psychiatry at the University of California School of Medicine. Dr. Sowers spoke on "The Psychology of Sex Hormones," and discussed the various stresses and emotional strains present in modern day living.

Southern California Society

The regular meeting of the Southern California Society of Hospital Pharmacists was held at the Daniel Freeman Hospital in Inglewood on March 9.

Mr. John B. Dames, a representative of Smith, Kline, and French Laboratories, spoke on "Prescriptions for Tomorrow."

Dr. Orville H. Miller from the faculty of the School of Pharmacy of the University of Southern California was the second speaker. He gave a resume and added comments to reports on the hearings of the Senate Anti-trust and Monopoly Subcommittee now being carried out in Washington.

Colorado Society

The first annual Seminar sponsored by the Colorado Society of Hospital Pharmacists in cooperation with the University of Colorado School of Pharmacy was held at the University of Colorado Medical Center in Denver on April 30.

The all-day program presented the following topics and speakers:

"The Role of the Pharmacist in Hospital Administration," by Dr. J. Horowitz, President, Colorado Hospital Association, and Administrator of the Denver General Hospital.

"The Future of Hospital Pharmacy Education in Colorado," by Dean C. H. Waldon, University of Colorado School of Pharmacy.

"Hospital Communications," by Sister Grace Marie, Administrator, St. Mary-Corwin Hospital, Pueblo.

"Prepackaging Procedures," by Mr. Herbert Carlin, Head, Pharmacy Department, University of Colorado Medical Center.

"Chemotherapy of Tuberculosis," by Dr. Irving Kass, Assistant Medical Director, National Jewish Hospital, Denver.

"The Pharmacy-Nursing Committee," by Mrs. Nelva Erickson, Nursing Supervisor, Denver General Hospital.

"Hospital Safety Practices and Procedures," by Mr. Samuel Kohan, Director of Pharmacy Service, Denver General Hospital.

"Dispensing Outpatient Prescriptions by Hospital Pharmacists"—a panel discussion with representatives of hospital administration, retail pharmacy, and hospital pharmacy.

"Hospital Formulary vs. *American Hospital Formulary Service*"—a panel discussion.

At a dinner following the Seminar, the members and guests heard Mr. Vernon O. Trygstad, President of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, speak on the future role of hospital pharmacy.

Illinois Society

On March 15 the Executive Committee of the Illinois Society of Hospital Pharmacists met to discuss and act on the recommendations of the Committee to Study Sponsorship. The Committee accepted the following recommendations:

1. The Illinois Society should apply for Institutional Membership in the Illinois Hospital Association.

2. The Society should utilize the facilities of the American Hospital Association Headquarters Building for its meetings and seminars.

3. The Society should undertake and conduct an annual Seminar as a part of its continuing educational program, and operate this Seminar on a self-liquidating basis.

4. The Society should undertake the preparation of an annual budget for the activities of the Society.

New officers of the Society announced at this meeting are: *President*, Mr. William R. Collins; *Vice-President*, Mrs. Kate M. Whitfield; and *Secretary-Treasurer*, Miss Mary Petersen.

Indiana Chapter

The regular quarterly meeting of the Indiana Chapter of the American Society of Hospital Pharmacists was held at Purdue University on April 12.

The following officers were elected to take office in June, 1960: *President*, Mr. Donald Friedmann, Vincennes; *Vice-President*, Mr. Ben Grubb, Logansport; and *Secretary*, Miss Mildred Wiese, Indianapolis.

Maryland Association

The April meeting of the Maryland Association of Hospital Pharmacists was held at the University Hospital in Baltimore.

Mr. Al M. Pawlina, Production Manager for E. R. Squibb and Sons, was the guest speaker. Mr. Pawlina discussed the development of penicillin from 1929 to the present.

Another portion of the program was a panel consisting of pharmacists and nursing educators. The topic for discussion was "Defining a Medication Error." Panelists were Mr. Abraham Wolfthal, Chief Pharmacist, U.S.P.H.S. Hospital, Baltimore; Mrs. Judith Morcels, Instructor in the School of Nursing, Maryland General Hospital, Baltimore; Mrs. Janis Kilmer, Instructor in the School of Nursing, University Hospital, Baltimore; Mr. Robert Statler, Pharmacy Specialist, Veterans Administration Central Office, Washington, D. C.; and Miss Ursula Heyer, Acting Chief Pharmacist, The Johns Hopkins Hospital, Baltimore.

Massachusetts Society

The Massachusetts Society of Hospital Pharmacists held its regular meeting on April 27 at the Worcester City Hospital.

The program included a panel discussion on "The Criteria for Judging the Reliability of a Manufacturer." Panelists were Mr. Joseph Barry, Worcester Memorial Hospital, Worcester; Mr. Arthur Thompson, Boston Children's Hospital, Boston; and Mr. Harry Brass, New England Medical Center, Boston.

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Dulcolax induces peristalsis by colonic contact alone, without systemic absorption.

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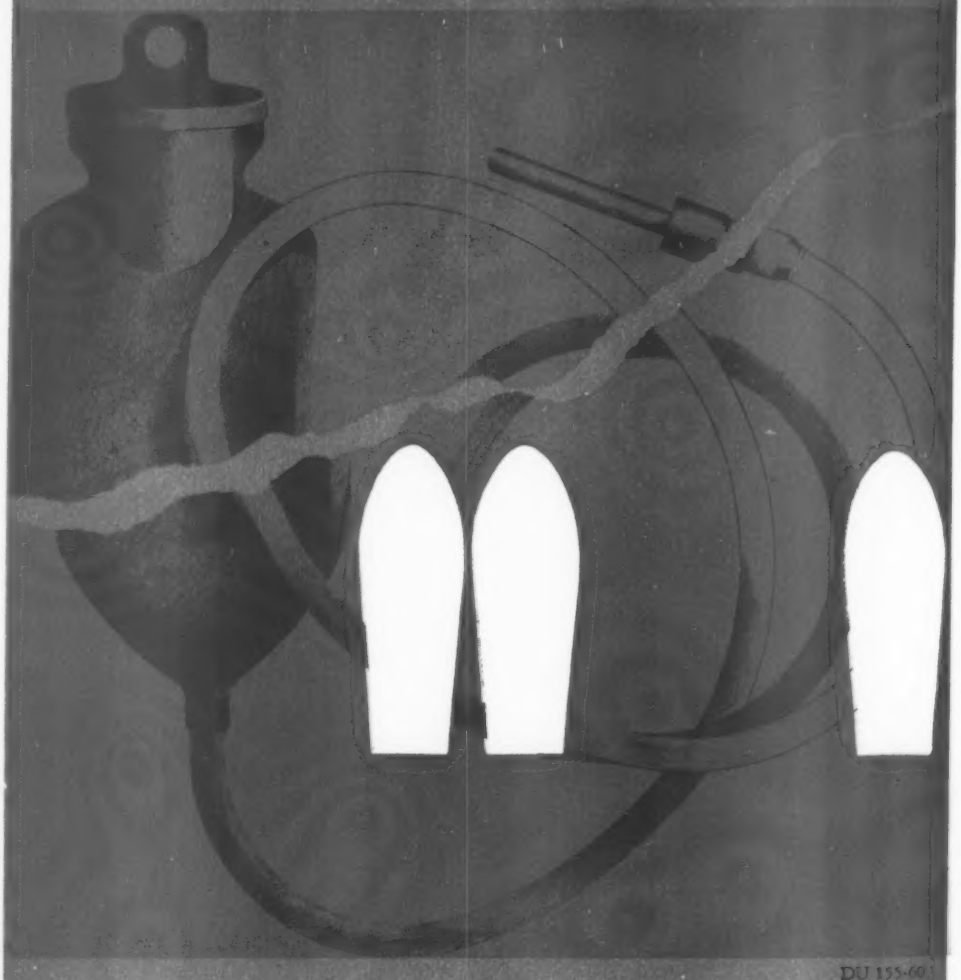

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Bottle of 100	6.00	3.60

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Michigan Society

The Michigan Society of Hospital Pharmacists held its regular meeting on April 28 at the Henry Ford Hospital in Detroit.

Dr. L. Ponka, Chairman of the Pharmacy Committee of the Henry Ford Hospital, was the speaker for the evening. Dr. Ponka spoke on the purpose and utilization of the Pharmacy Committee, its organization, and limits of its responsibility. Following this presentation by Dr. Ponka, there was a general discussion on the rules and regulations covering pharmacy committees in the member hospitals.

Oklahoma Society

The Oklahoma Society of Hospital Pharmacists held its regular meeting on April 21 at the St. Anthony Hospital in Oklahoma City.

The speaker for the evening was Dr. David Mock, Head of the Department of Investigational Research and Therapeutics of the Oklahoma Veterans Administration. Dr. Mock spoke on "A Plan of Research and Administration," using as examples of research, work done on cholesterol, diuretics, and other drugs. He described the teamwork necessary on such projects, and explained the double-blind system of investigation. Dr. Mock supplemented his talk with colored slides to illustrate the techniques described.

Tennesssee Society

The Tennessee Society of Hospital Pharmacists held its annual meeting and Seminar at the University of Tennessee College of Pharmacy on April 16. The Seminar was sponsored jointly by the Society and the College of Pharmacy.

The program presented the following speakers and topics: "Current Trends in Hospital Care," by Dr. Frank S. Groner, Administrator, Baptist Memorial Hospital, Memphis, and President-Elect, American Hospital Association.

"Utilizing Statistics in Hospital Pharmacy Management," by Mr. Clifton J. Latiolais, Director of Pharmacy Service, Ohio State University Health Center, and President-Elect, American Society of Hospital Pharmacists.

"The Current Status of the *American Hospital Formulary Service*," by Dr. William M. Heller, Director of Pharmacy Service, University of Arkansas Medical Center, and Director, *American Hospital Formulary Service*.

"Formulation Problems in Ointment Bases," by Dr. Joe E. Haberle, Assistant Professor, University of Tennessee College of Pharmacy.

"Simplified Methods of Identifying Narcotic Alkaloids," by Mr. W. B. Swafford, Assistant Professor, University of Tennessee College of Pharmacy.

"The Hospital Teaching Program at the University of Tennessee," by Mr. William Djerf, Instructor, University of Tennessee College of Pharmacy.

At the business meeting following the Seminar, the following officers were elected to serve for the coming year: *President*, Mr. Owen Crutcher, Memorial Hospital, Johnson City; *Vice-President*, Mr. William Djerf, University of Tennessee College of Pharmacy, Memphis; *Secretary*, Miss Jane Bratton, St. Thomas Hospital, Nashville; and *Treasurer*, Mr. William Upchurch, Methodist Hospital, Memphis.

New Jersey Society

The April 21 meeting of the New Jersey Society of Hospital Pharmacists was held at the offices of Hoffmann-La Roche, Inc., in Nutley.

Mr. Thomas Brown, General Sales Manager of Roche Laboratories, moderated a panel-symposium program which included the following topics and speakers from Roche: "The Importance of the Hospital Pharmacist," by Mr. Parke Richards, Jr., Director of Sales Operations; "Things to Come," by Dr. Emmanuel Grundberg, Director of the Chemotherapy Department; and "What's Going on in Washington?" by Mr. Daniel Byles, Attorney.

New officers of the New Jersey Society are: *President*, Mrs. Florence Frick: *Vice-President*, Mr. Henry Roche; *Secretary*, Miss Joyce Dolecki; and *Treasurer*, Mr. Victor Ern.

Kansas City Society

The Society of Hospital Pharmacists of Greater Kansas City held its regular meeting on March 7 at the Blue Cross-Blue Shield building in Kansas City.

The program included a film and discussion on the artificial kidney. The film was supplied by Baxter Laboratories.

Greater New York Chapter

The Greater New York Chapter of the American Society of Hospital Pharmacists met at the Frances Schervier Home and Hospital on the afternoon of April 7.

Dr. Vincent Squilla, psychiatrist at Frances Schervier Home and Hospital, was the speaker. The title of his presentation was "Psychic Energizers." Dr. Squilla gave a background of the physiology of mental depression and then described the role of monoamine oxidase inhibitors and thymolytic agents in the treatment of this disorder.

Northeastern New York Society

The Northeastern New York Society of Hospital Pharmacists, in cooperation with Pfizer Laboratories, held a Seminar at the Albany Hospital in Albany, New York, on May 7.

The program included these topics and speakers:

"Strip Packaging," by Mr. Robert Bogash, Director, Pharmacy Department, Lenox Hill Hospital, New York City.

"Flexible Standards and Their Effect on the Teaching of Pharmacology in Nursing Curriculum," by Sister Mary John Baptist, Assistant Director of Nursing Education, St. Peter's Hospital, Albany.

"Current Trends and Practices in Cancer Research," by Dr. Kenneth B. Olsen, Director, Sub-Department of Oncology, Albany Medical College, Union University, Albany.

"Utilizing Statistics in Hospital Pharmacy," by Mr. Clifton J. Latiolais, Director of Pharmacy Service, Ohio State University Health Center, Columbus, Ohio.

"The Hospital Pharmacist's Additional Responsibilities," by Sister Mary Gonzales, R.S.M., Director of Pharmacy Service, Mercy Hospital, Pittsburgh, Pennsylvania.

"The Hospital Administrator Views His Pharmacist," by Mr. Ferdinand Haase, Jr., Medical Director, Albany Hospital, Albany.

"The Status of Pharmacy Reciprocity in the State of New York," by Mr. Kenneth Griswold, Secretary of the Board of Pharmacy, State of New York.

"Review of Current Legislation with Respect to Hospitals," Mr. Charles M. Royle, Executive Director, New York State Hospital Association, Albany.

"Target for Tomorrow," by Mr. Vernon O. Trygstad, President of the American Society of Hospital Pharmacists.

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Southeastern New York Society

The regular meeting of the Southeastern New York State Chapter of the American Society of Hospital Pharmacists was held at the Lenox Hill Hospital in New York City on March 24.

The results of the recent election were announced. New officers are: *President,* Mr. Leo Blackman; *Vice-President,* Mr. Ben Kaufman; *Secretary,* Mr. Joel Yellin; and *Treasurer,* Miss Goldie Goldman.

Mr. Robert Bogash, Director of Pharmacy Service at Lenox Hill Hospital and Past-president of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, was speaker for the evening. His topic was "Hidden Costs in Dispensing." Mr. Bogash discussed such points as purchasing practices, receiving procedure, storage, prepackaging, inventory control procedures, and many other considerations that figure into the total cost of operations.

Utah Society

The regularly scheduled educational meeting of the Utah Society of Hospital Pharmacists was held at the Veterans Hospital, Fort Douglas, Utah, on March 26.

The first speaker was Mr. Duane Allen, of Smith, Kline, and French Laboratories. Mr. Allen spoke on the role of research by the pharmaceutical manufacturers.

Dr. Edward C. Beck, a practicing clinical psychologist, was the second speaker. Dr. Beck talked about basic research in the field of neurology. He discussed a study in which scientists have attempted to locate the action of tranquilizers in certain areas of the brain.

The presentations were followed by a general discussion period.

Southern Appalachian Society

The Southern Appalachian Society of Hospital Pharmacists met in Huntington, West Virginia for its regular quarterly meeting on April 19.

The featured speaker at the meeting was Mr. Vernon Trygstad, President of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. Mr. Trygstad spoke on the role of the pharmacist in recruitment, and especially the active part the hospital pharmacist should play in this function. He also stressed the necessity for hospital pharmacists to contribute to both state and local pharmacy organizations.

The new officers in the Southern Appalachian Society are: *President,* Mr. Joseph Silverman; *Secretary,* Mr. Morris Freidman; and *Treasurer,* Mrs. Dolores Dodd.

Wisconsin Society

The Wisconsin Society of Hospital Pharmacists met at Milwaukee Children's Hospital for its regular meeting on March 18.

Dr. John C. Peterson, Pediatrician-in-Chief at Milwaukee Children's Hospital, was the speaker for the program, which was devoted to poison control and the development of poison control centers. Dr. Peterson gave a historical sketch of the establishment of the Control Center at Milwaukee Children's and described the method of operation. He closed his presentation with a group of statistics indicating that the creation of poison control centers has helped materially in the reduction of deaths due to accidental poisoning.

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Because of the infrequency of the disease in this age group, its sudden onset, the profusion of inconsistent presenting symptoms, and because the accompanying symptoms of anorexia and vomiting are also characteristic symptoms of many other ills of infancy.

Source: Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.: Diabetes *8*:289, 1959.

for those pediatric puzzlers..."A routine urinalysis and blood sugar should be done whenever the possibility of diagnosing diabetes is entertained."*

DIABETES MELLITUS AT AGES 1 TO 5

Order of Frequency of Presenting Symptoms in 110 Patients

Symptoms	No. of Patients	Per cent of total group
Polyuria	93	84.5
Polydipsia	89	81.0
Weight loss	47	42.7
Polyphagia	28	25.4
Anorexia	16	14.5
Lethargy	14	12.7
Enuresis	7	6.4
Vomiting	5	4.5
Irritability	3	2.7
"Craving for sweets"	3	2.7
"Sticky diaper"	3	2.7
"Strong odor to urine"	2	1.8
Glycosuria	2	1.8
Hypoglycemia	2	1.8
Personality change	1	0.9
Boils	1	0.9
Headache	1	0.9
Abdominal cramps	1	0.9

Adapted from Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.*

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BROADSWORDS are not standard equipment in Hospital Pharmacies these days . . . nor do rising costs roam your hospital's corridors in the form of flesh-and-blood dragons.

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• *A 32-page illustrated brochure "Sterile Fluids for the Hospital" will prove interesting to every Pharmacist. Request your copy of MC-513R TODAY.*

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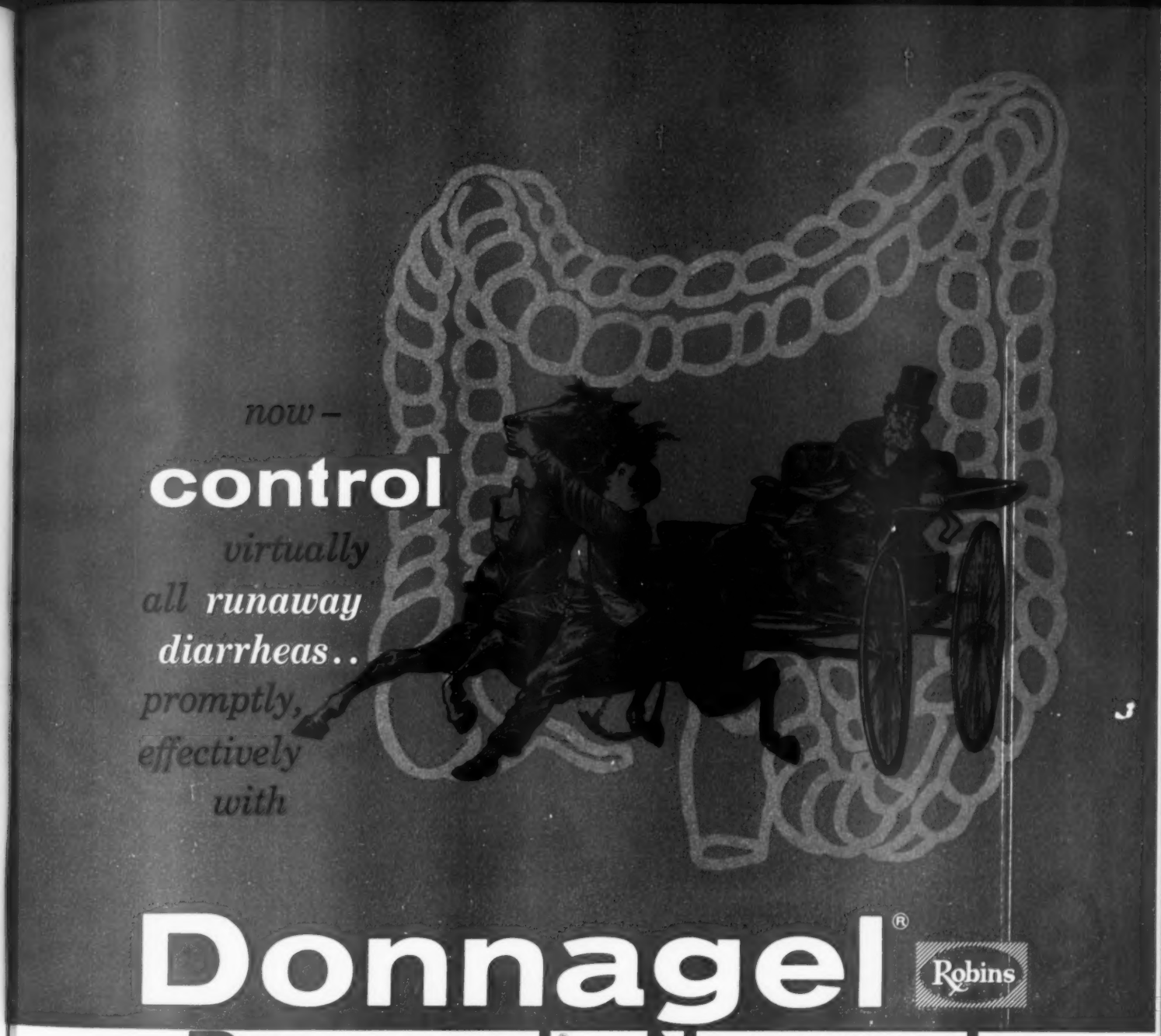

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Kaolin (90 gr.)	6.0 Gm.
Pectin (2 gr.)	142.8 mg.
Hyoscyamine sulfate	0.1037 mg.
Atropine sulfate	0.0194 mg.
Hyoscine hydrobromide	0.0065 mg.
Phenobarbital (¼ gr.)	16.2 mg.

DONNAGEL WITH NEOMYCIN

Same formula, plus

Neomycin sulfate	300 mg.

(Equal to neomycin base, 210 mg.)

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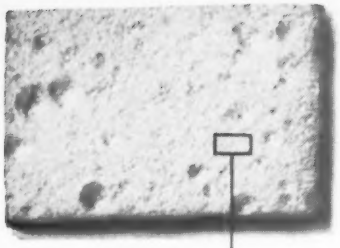
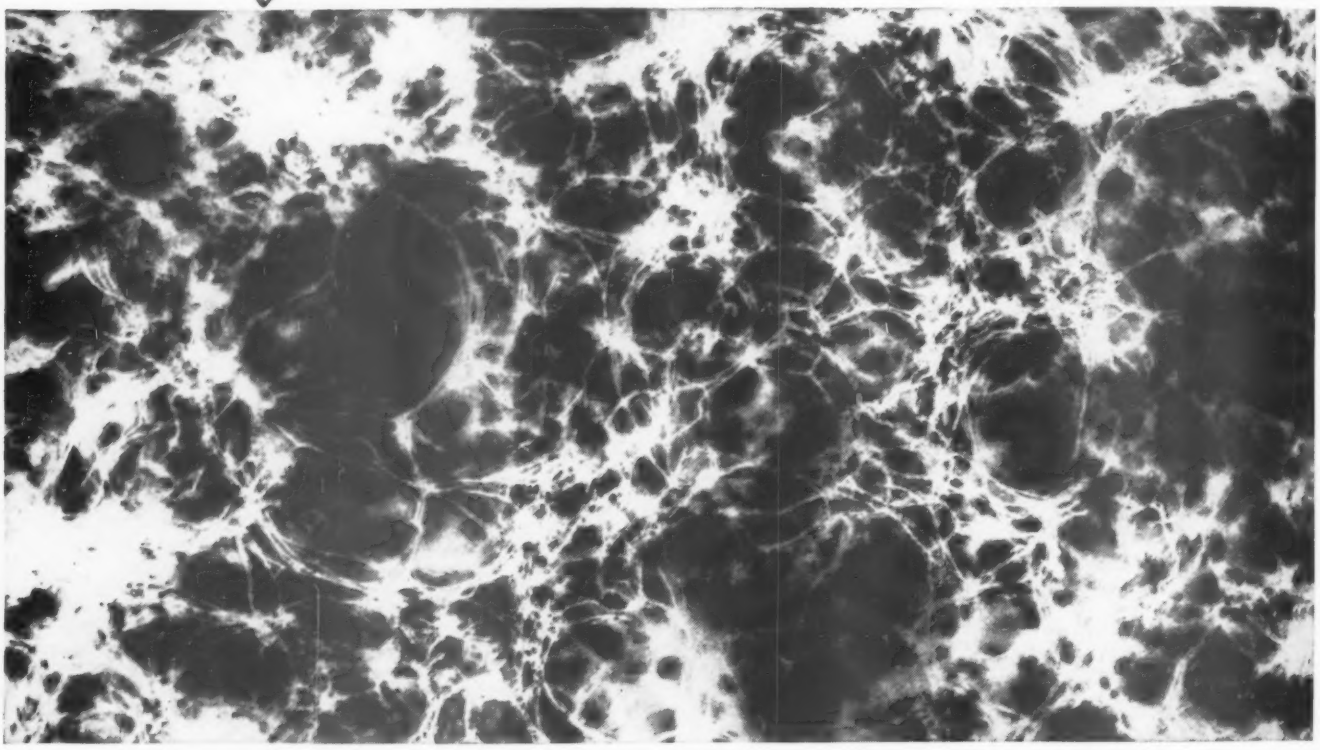


here blood
enters...
stops...
clots...

Cross section of Gelfoam magnified 50 times



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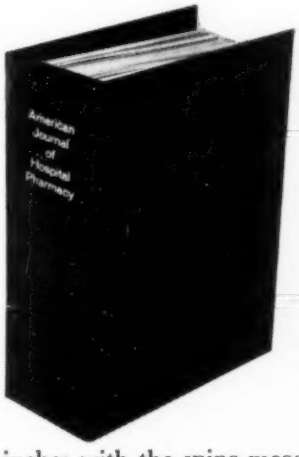

A loose-leaf binder for the AMERICAN JOURNAL OF HOSPITAL PHARMACY is now available from The Hamilton Press, Hamilton, Illinois. The new binder has been designed for THE JOURNAL and will hold the twelve issues satisfactorily. The binder is brown in color and "American Journal of Hospital Pharmacy" is embossed on it in gold. The binder is 9 by 12¼ inches with the spine measuring 4 inches.

The cost of the binder is four dollars ($4.00) each and orders may be directed to The Hamilton Press, Hamilton, Illinois.

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PROFESSIONAL DIVISION

newsletter

SIXTH OF A SERIES WITH SIGNIFICANT SUGGESTIONS FOR CONTROLLING CROSS INFECTION

THANKS so much for requesting so many reprints of the earlier issues of STAPH NEWSLETTER. As you will note above, this is the sixth of a continuing series. We have replenished our supply and will be glad to send you individual ones or the complete set. Just let us know which you prefer.

Did you know that the new Ninth Edition (1960) of "Control of Communicable Diseases in Man" now recommends standard regulations for prevention and control of hospital-acquired staph infections? Preventive measures emphasize strict aseptic technics and close coordination of all hospital control activities through your own Infections Committee. Paragraphs on reporting known staph infections to local public health authorities include, "2 or more concurrent cases on same hospital service or ward are to be regarded as an epidemic".

We do not have copies of this book but, if your library does not have it yet, it is available from the American Public Health Association, 1790 Broadway, New York 19, N.Y. (paper bound, $1; de luxe, $2.50).

Until recently our mail brought frequent queries on the "why" and the "what-to-do" of controlling staph through disinfection of the environment. Now, more and more requests are for specific instructions on "how to" disinfect efficiently.

So you'll be glad to hear that we have just completed a set of eight 3" x 9" "How-to-use" cards on O-syl®—with specific dilution and timing recommendations. Individual cards cover: general environmental disinfection; tuberculosis hygiene; disinfection of thermometers, of instruments, of catheters; disinfection in the operating room, in food service areas; and disinfection of blankets, linens, and diapers. Each card is handy for teaching and for posting. We'll be glad to send you as many sets of cards as you need—or, if you prefer multiple copies of one particular card, let us know when you write.

Dr. Ralph Adams' newest report on "Sterility in Operating Rooms" appeared in the March, 1960, issue of Surgery, Gynecology and Obstetrics. "At the end of 12 months, there had been 2 clean wound infections in 800 cases, 0.25 per cent." Culture plate illustrations reconfirm his contention that, "Sterility in operating rooms can be maintained solely by frequent repetition of bactericidal cleaning processes (disinfectant-detergent plus mechanical), isolation by physical barriers from the rest of the hospital, and bacteriologically protective coverage of surfaces which cannot be sterilized".

Lehn & Fink's Tergisyl® is the disinfectant-detergent used in this continuing study. Amphyl® disinfectant is used on all blankets.

A review of bacterial endocarditis cases covering ten years (1949-1958) at the Bailey Thoracic Clinic in Philadelphia revealed a significant increase in cases in the last 5 years, and, even more significantly, an increase in mortality. With the staphylococcus having replaced Streptococcus viridans as the causative agent, the study by Lisan and his co-workers (American Heart Journal, page 184, February, 1960) indicates not only that "cardiac surgery predisposes the valves and endocardium to superimposed staphylococcal infection" but that "resistant strains of staphylococci found in hospitals apparently have a predisposition for the endocardium of postsurgical patients".

Have you seen the annotated bibliography on control of staph infections published in the American Journal of Nursing, December, 1959? As far as we know, it is the most comprehensive review of available articles made to date. Pertinent films and books are also mentioned. This bibliography could be very valuable to your Infections Control Committee. We have a limited number of them available and will be glad to send you one. Please write soon.

The other day I used the word "sterilize" when talking to an O. R. Supervisor about L&F Instrument Germicide. Her immediate query was, "How can instruments be 'sterilized' by chemical disinfection which does not kill spores?" Here's how—Heat the L&F Germicide to the boiling point, immerse instruments for 20 minutes in the boiling germicide. This destroys resistant bacterial spores and viruses, including those of serum and infectious hepatitis. Of course, boiling water alone would not sterilize within any practical period of time, that is, in less than four hours. Boiling L&F Germicide sterilizes in 20 minutes. May we send you our new folder on this product?

Lehn & Fink's Amphyl®, O-syl®, and Lysol® disinfectants, Tergisyl® detergent-disinfectant, and Instrument Germicide are broad spectrum, nonselective synthetic phenolic compounds which are widely microbicidal, including staphylocidal, pseudomonacidal, fungicidal, and tuberculocidal.

If you have a baffling infection problem, why not discuss it with us. Perhaps our technical advisors and research laboratories could help. And I, personally, would appreciate hearing from you.

Charles F. Manz
General Sales Manager
Professional Division

LEHN & FINK PRODUCTS CORPORATION
4934 LEWIS AVENUE, TOLEDO 12, OHIO

Dear Sirs:

From Abroad

DEAR SIRS: As regards the article "Pharmacy and Outer Space" which appeared in your JOURNAL (December 1959), with your permission, we have translated it into Japanese for reproduction in the *Yakuji Nippo* (Pharmaceutical News). This appeared in the April 2 issue of our Journal, No. 2772.

KENJI TAKADA, *Editor*

Yakuji Nippo-Sha, Ltd.
(Pharmaceutical News)
1-43, Jinbocho, Kanda,
Chiyodaku, Tokyo

DEAR SIRS: I wish to inform you that we are the only subscriber of your periodical in our country and as it is the only world journal of hospital pharmacy, we want to have all numbers.

PHMR L. KUNOVSKY, *Chief of Pharmaceutical Development Centre*

Rozvojové Lékarnické Stredisko
Prague, Czechoslovakia

Courses in Radio-Pharmaceutical Usage and Practice

DEAR SIRS: During the past several years, there has been evidenced an increase in the number of hospital pharmacists who indicate some degree of interest in radio-pharmaceutical usage and practice. Frequently, I have been asked questions concerning the availability of short term training courses in this general field. As you may know, the Division of Radiological Health of the United States Public Health Service provides for interested professional personnel in the broad field of public health, a number of such courses. It would seem appropriate, therefore, to announce in the JOURNAL the several courses which I have enumerated below. Interested hospital pharmacists should direct inquiries for further information on these subjects to the Chief, Training Program, Robert A. Taft Sanitary Engineering Center, U. S. Public Health Service, 4676 Columbia Parkway, Cincinnati 26, Ohio. The courses, scheduled dates, and the locations at which they will be offered are as follows:

BASIC RADIOLOCAL HEALTH

Cincinnati, Ohio—October 3-14, 1960
Cincinnati, Ohio—January 23-February 3, 1961
Cincinnati, Ohio—March 13-24, 1961
Montgomery, Alabama—September 12-23, 1960
Las Vegas, Nevada—February 6-17, 1961

RADIONUCLIDE PROTECTION

Cincinnati, Ohio—October 17-21, 1960

ORIENTATION IN RADIOLOGICAL HEALTH

Cincinnati, Ohio—January 9-20, 1961

MEDICAL ASPECTS OF RADIOLOGICAL HEALTH

Cincinnati, Ohio—November 28-December 9, 1960

While the content of these courses is not specifically directed toward hospital pharmacy practice, the information which may be derived through participation in these training periods can very definitely be applied to one's professional practice. I should be pleased to discuss this matter with any hospital pharmacist who is contemplating such endeavor.

Thank you for your attention to this matter.

WILLIAM H. BRINER, *Chairman*

ASHP Committee on Radio-Pharmaceuticals
National Institutes of Health
Clinical Center
Bethesda, Maryland

Comment from PMA on Editorial

DEAR SIRS: Your editorial, "Physicians in Quandaries," which was published in the AMERICAN JOURNAL OF HOSPITAL PHARMACY for February 1960, has been read with interest by our staff. It is gratifying to us that you have considered it important to bring this timely discussion of drugs and the pharmaceutical industry to your many readers . . .

ROBERT J. BENFORD, M.D.
Director of Medical Relations

Pharmaceutical Manufacturers Association
1411 K Street, N.W.
Washington 5, D. C.

Correction in Therapeutic Trends

DEAR SIRS: May I call your attention to a typographical error in the section, Therapeutic Trends? In the April issue, page 240, under the title "Treatment of Intestinal Gas . . ." the drug used was Methyl Polysiloxane which is misspelled in all cases.

WILLIAM JOHNSON, *Editor*

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Bronson Methodist Hospital
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by DON E. FRANCKE

Proprietary and Nonproprietary Names for Drugs

► IN THE PRESENT CONFLICT OF OPINION over proprietary and nonproprietary names for drugs it is often overlooked that both names have a definite place and usefulness. It is likewise unfortunate that the remarks of those who speak in favor of nonproprietary names are interpreted as *opposing* trade names. This is not the case. Nor is it true that hospitals, which are among the foremost advocates of *accepting or adopting* drugs under their nonproprietary names, do not *use* trade name drugs in filling prescriptions. The record of sales to hospitals by the major pharmaceutical firms should disprove this fallacy.

But there is another matter which is of fundamental importance and this is the professional responsibility of the pharmacist. In the final analysis, the pharmacist is responsible for the strength, quality, and purity of the drugs he dispenses. This responsibility is so important it is emphasized in the *Minimum Standard for Pharmacies in Hospitals* which states ". . .The pharmacist in charge shall be responsible for. . .specifications both as to quality and source for purchase of all drugs, chemicals, antibiotics, biologicals and pharmaceutical preparations used in the treatment of patients. . ." This is a responsibility a pharmacist cannot avoid; it is one of the prime professional responsibilities which justifies his licensure. And herein lies the crux of the controversy of proprietary *vs* nonproprietary names.

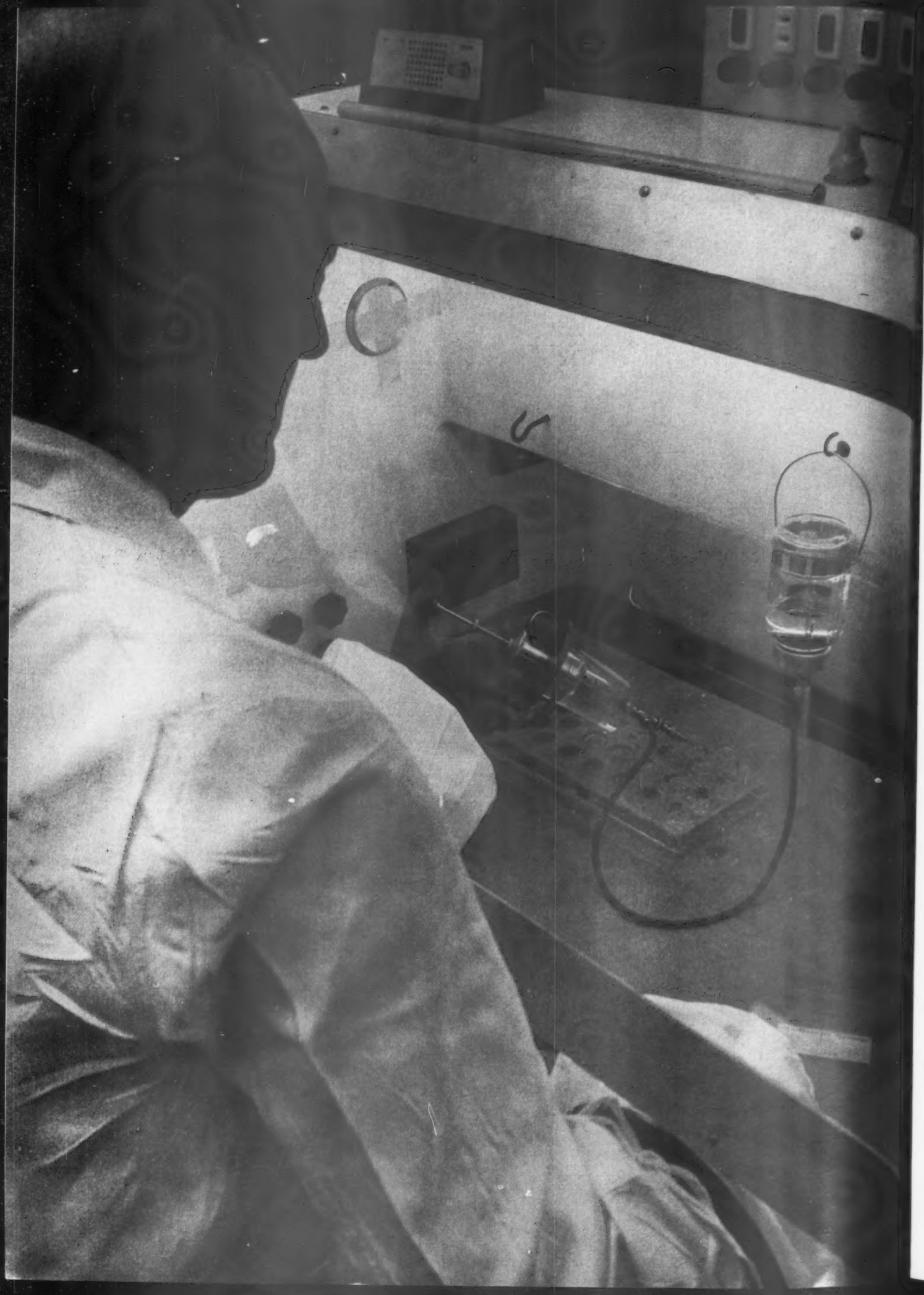
However, confusion exists here, too, for it is not really a question of drug *names;* it is a question of drug quality. True, there is often a direct relationship between a trade name and quality. This, in fact, is one of the main justifications for the existence of trade names. Trade names function not so much to describe a drug as to identify its producer. On the other hand it is a mistake to infer, as so many today are implying, that because a drug is sold under its nonproprietary or generic name, it is *ipso facto* of inferior quality. To test this, one has only to refer to the catalogs of the major pharmaceutical houses and to note the large percentage of their products sold under generic names. Thus the quality of the drug is not dependent upon its name, but rather upon the integrity of its producer.

How then is the hospital pharmacist to assure the quality of the product he dispenses? The most commonly used method is by designating acceptable sources of supply—pharmaceutical houses with integrity. Some of these will use a trade name for an official product, others will use a nonproprietary name. The important consideration in this case is not so much the name under which the drug is distributed but, rather, the reputation of the house for quality. It is also a reason to stress the specialized knowledge which only the pharmacist possesses. This specialized knowledge marks the pharmacist as unique and is pharmacy's principal justification for being called a profession. A profession can be maintained and strengthened only as its practitioners continuously utilize their specialized knowledge and, in turn, receive from others an acknowledgement of their superior education, training, and judgement in the area encompassed by their specialty.

Rigid specifications are also important in the purchase of drugs but it must be emphasized that the pharmacist must personally inspect the product before accepting it. It is quite possible for a medicinal to assay at 100 percent potency and still not be therapeutically effective if its *pharmaceutical properties* are not correct. This is another reason for stressing the importance of reliable sources of supply.

It is unfortunate that American pharmacists lack a tradition of testing drugs purchased and those prepared in the pharmacy. True, the development of a complete control laboratory is beyond the scope of the majority of pharmacies. But, at the same time, it is within the scope of many of the larger pharmacies and it is highly desirable that more pharmacies establish assay and control as an integral part of their functions. A significant amount of assay and control can be done even in the smaller pharmacies. Increased emphasis by hospital pharmacists on assay and control procedures would help to assure the quality of drugs dispensed.

Within the framework, then, of reliable sources of supply, rigid specifications, and inspections and assay, the pharmacist can effectively exercise his professional responsibility for the quality of drugs he dispenses. In the exercise of this responsibility he will use both nonproprietary and proprietary names. However, the type of name used will not be as significant as the integrity of the supplier. In no event should quality be sacrificed for price—nor need it be—though both proprietary and nonproprietary names are used and will continue to be used in hospitals.



Aseptic transfer of phosphorus-32 using a plastic-shielded Cornwall pipette with ¼" lead ring to reduce bremsstrahlung, the entire procedure taking place within an ultraviolet hood

NUCLEAR MEDICINE HAS COME OF AGE

by WILLIAM H. BRINER

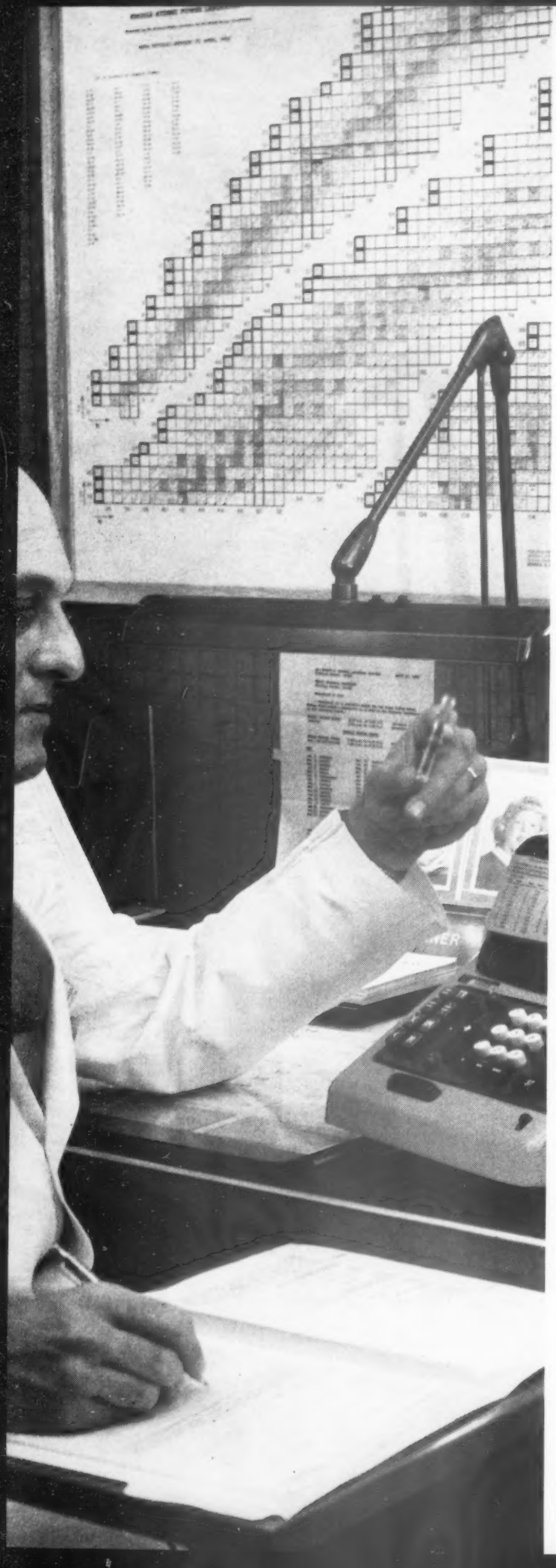
► SELDOM IN THE HISTORY OF MEDICAL PRACTICE IN the United States has there been established so rapidly a completely new means of diagnosis and treatment of certain pathologic conditions of man as has been evidenced by the use of radio-pharmaceutical products. When one considers, for example, that so recently as August 2, 1946, the first shipment of a radioisotope from the Isotopes Branch of the Manhattan Engineering District at Oak Ridge, Tennessee, was directed to the Barnard Free Skin and Cancer Hospital in St. Louis, Missouri,[1] and, when one examines recent figures released by the Atomic Energy Commission to the effect that at the end of 1958, there were approximately 2,000 licensees in the medical institution or physician category,[2] it is not at all difficult to rationalize this statement. Further, it has been estimated[3] that in excess of one million patients received radiopharmaceutical products last year. Truly, this indicates extremely rapid growth in a highly complex field.

WILLIAM H. BRINER is Chief, Radiopharmaceutical Service, Pharmacy Department, Clinical Center, National Institutes of Health, Bethesda 14, Maryland.

Presented at the Hospital Pharmacy Seminar sponsored by the Maryland Association of Hospital Pharmacists, Bethesda, Maryland, November 24, 1959.

A Positive Approach for Pharmacy

The impact of this widespread utilization of these materials has been felt in the medical profession for a number of years. Unfortunately, this is not the case with pharmacy, for, at the present time, only



Calculator and slide rule simplify completion of required computations
NATIONAL INSTITUTES OF HEALTH PHOTO

a handful of pharmacists in even fewer pharmacy departments throughout the country are directly concerned with the administration of radioactive materials in human subjects. In addition, there are many individuals within our profession who believe that pharmacy has no place in a hospital radioisotope program, that to engage in radiopharmaceutical procedures only serves to detract from the primary functions of a hospital pharmacist. It shall be my purpose, in the course of this dissertation, to take exception to such negative philosophy, and to point out only a few reasons for a more positive approach to this problem.

Certain facts are self-evident. Almost five years ago, the *United States Pharmacopeia* recognized certain of the more widely used radioisotope products as medicinal agents; there are a number of monographs for radiopharmaceutical products in the Fifteenth Revision of this compendium. There is no reason to doubt that more and more of these materials will receive official recognition in the future.

In addition, two well known pharmaceutical manufacturers have already established radiopharmaceutical departments for the production and sale of radioactive medicaments to authorized individuals or institutions. Although both companies supply numerous

products ready for administration to patients, there still frequently exists a need at the hospital level to modify these products in order to more closely meet the needs of the individual patient and satisfy the requirements of the individual physician. While in most cases, this modification merely consists of a dilution of the commercial product, in some cases, it is a considerably more complex procedure.

Pharmaceutical Aspects

Admittedly, these two pharmaceutical manufacturers offer a great deal in the way of service and in the variety of radioisotopic products which they have made available to duly authorized institutions or clinicians. However, it is economically just not feasible for them to supply every size dose of every dosage form of all the radioisotopes which are used in medicine today, any more than it is possible for them to supply all such products of a non-radioactive nature. Actually, there is an imposing number of radioisotopes utilized in medical practice today, whether in research, diagnosis or therapy, which are not commercially available as radiopharmaceutical products. These materials may be procured either from one of the National Laboratories, such as Oak Ridge National Laboratory, which is operated by a private industrial firm under contract with the Atomic Energy Commission, or from any one of several radiochemical suppliers. In either case, individuals or institutions who wish to procure these materials for use in humans are required to possess a license issued by the Atomic Energy Commission.

Here, however, there is one further consideration which is of great significance to us as pharmacists. The AEC has wisely imposed a number of conditions which must be satisfied before a license will be granted to a prospective medical user. In the case of those radiopharmaceutical products supplied by commercial pharmaceutical sources, the guarantee of pharmaceutical quality and assay of these products is, of course, made by the producer. However, a standard condition of the AEC states that if radioisotopes are to be procured for human use from other than a reputable pharmaceutical supplier, the licensee must show proof of his ability, or the ability of someone in his institution or organization, to determine the pharmaceutical quality and radiochemical assay of such material before it may be administered to human patients, or, in fact, before the license from the AEC can be granted. I submit to you that there is no one in a hospital more professionally qualified to attest to the pharmaceutical quality of a given preparation than is the hospital pharmacist. If, for the moment, we can look upon these products only as pharmaceutical entities, and nothing else, this approach is more clearly defined. This is to say that when a pharmacist considers a product from the standpoint of pharmaceutical quality, he does not merely check the reports of assay of the active constituent. He looks a bit further into such matters as the vehicle in which the product has been formulated; he determines the relative acidity or basicity of the product by observing the *p*H; if an oral product is involved, the matter of patient acceptability is considered; if a parenteral product, he examines the product critically to detect any particulate material which may be present, and determines that the product is pyrogen-free and sterile, and other equally important factors. Obviously, what I am saying is that the pharmacist scrutinizes the whole product, not just one aspect of it, in determining whether or not this product is suitable for administration to human subjects.

Now, if we go one step beyond this point in our thinking, many of the conditions which a good pharmacist finds unacceptable in a pharmaceutical product can be avoided through the use of proper techniques in the formulation of the product. If we may consider parenteral products for the moment, most pharmacists are acutely aware of the ever present possibility of introducing pyrogenic contamination into a product, and of certain means of avoiding such contamination. A pharmacist is also cognizant of such things as the adsorptive properties of certain filtration media, whether they are used for clarification or sterilization of the product. When one considers that frequently in the formulation of a radiopharmaceutical product, the active constituent is represented by only a fraction of a microgram of dissolved material, it becomes apparent that adsorption is a phenomenon which deserves critical attention. It can be said that pharmacists, generally, are well aware of the physical and chemical properties of the materials encountered in their practice.

Need for Professional Advice

That certain other professional disciplines may not be so aware of some of these considerations may be illustrated with several examples. I am reminded of the technician who consulted me several years ago concerning a sulfur-35 solution he had sterilized for use in some animal experimentation to be undertaken by his laboratory. The radiochemical analysis of the solution after sterilization, when compared with the initial assay of the material, indicated that approximately 95 percent of the radioactive sulfur had disappeared somewhere in the procedure. Upon discussing the matter with him, the fact that he had used a Seitz filter pad to effect sterilization was determined, and, needless to say, it was on this pad that the wayward sulfur-35 was discovered.

Perhaps even more remarkable, is the physician who attempted to dissolve a capsule containing sodium radioiodide in a hydrochloric acid solution for subsequent administration, after neutralization of the acid, to a child who was unable to swallow the capsule. The clinician soon discovered the error of his ways when he found, much to his consternation, that in his attempts to solubilize the capsule, most of the iodide present was oxidized, and the resultant iodine volatilized. The radioactive iodine, of course, was inspired by this individual, and it eventually found its way to his own thyroid gland.

In another case, a physician took great pains to add sterile, pyrogen-free diluent to a carbohydrate labeled with carbon-14, which had been received from a radiochemical supplier. The solution was then allowed to stand at room temperature for several days prior to its administration to a patient. The patient, after receiving an intravenous dose of the material, experienced a fairly severe pyrogenic reaction.

Consultation As a Minimum

I mention these examples only to point out the many pitfalls to be encountered when non-pharmacists formulate pharmaceutical products. It is in this area of product formulation or modification that the hospital pharmacist has much to offer in assistance to those responsible for the radioisotope program in the hospital. This assistance may be given in the form of consultation. In these cases, the hospital pharmacist requires little or no additional training beyond the basic pharmacy education and his study or experience in the hospital pharmacy specialty. When functioning as a consultant to others who will actually be carrying out his recommendations, the pharmacist may advise on matters related to the vehicle of the product; aseptic procedures which may be required to modify a given product, or to repackage in smaller units the original bulk product; the proper choice of a chemical or bacterial preservative compatible with other substances in the product; and many other considerations of a strictly pharmaceutical nature. This aspect of consultation is one which is often overlooked when radioisotopes are concerned, but it is in no way less applicable than a similar consultation involving a non-radioactive compound. Frequently, all that is required to effect so mutually a beneficial agreement is the offer from the pharmacist to assist. In so doing, he broadens significantly the scope of operation of his department, and enhances the professional standing of the department within the hospital.

Active Assistance by Hospital Pharmacist

In other cases, and this is the area where pharmacy is sadly lacking at the present time, the assistance given by a pharmacist may be very active in nature. That is, the actual formulation or modification of products is accomplished within the pharmacy department by pharmacy personnel. It is in this type of operation where hospital pharmacists with additional specialized training in radioisotope techniques and radiological health disciplines may offer a sorely needed service. Procedures involving radioisotopes cannot be compared directly with any other type of pharmaceutical endeavor. This is not to say that many of the techniques utilized are not the same as those used in other procedures more common to routine pharmacy operations. For example, the care which is required in order to avoid radioactive contamination has often been compared with similar diligence employed during certain bacteriological manipulations; and this is perhaps a valid comparison. Similarly, radioisotopes react chemically in just about the same manner as do their non-radioactive counterparts, so that predictions concerning such matters as incompatibilities and product stability can be applied equally well with such materials. However, there are certain differences, too, between work with a radioisotope and work with a stable, or non-radioactive isotope of a given chemical element. Many substances exhibit a chemical toxicity. However, this effect is demonstrable only if the material comes into contact with the skin or is somehow taken into the body. Some radioisotopes, on the other hand, need not come into actual physical contact with the body to be toxic. This manifestation may become apparent even when one is at some distance from the material, and this is, in fact, the case with a gamma emitting isotope. In addition, the old saying, "here today and gone tomorrow," may well apply to radioisotopes, for, although theoretically a radioactive isotope never completely decays, certainly from a practical standpoint, with a short half-life material, one may well have a significant amount of it present one day, and very little remaining the next, due to the radio-active decay of the isotope. These, then, are only some of the differences to be noted in work with radioisotopes.

Training Opportunities

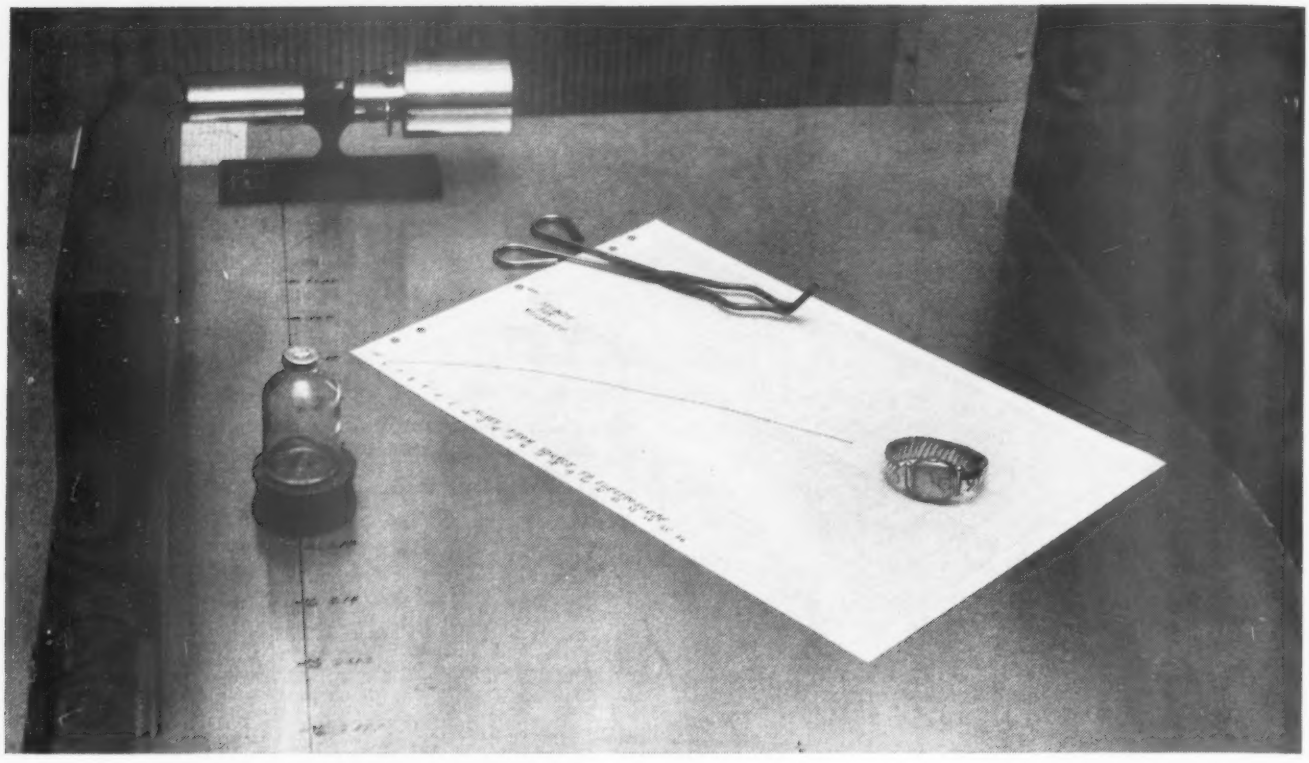
Perhaps the greatest deterrent to more pharmacists becoming engaged in an active way in radiopharmaceutical programs has been the lack of, or at best, the scarcity of suitable training programs which will prepare them for such endeavor. This situation is one which is being given serious consideration by several groups, not the least of which is the American Society of Hospital Pharmacists. The Society has, for a number of years, had a special comittee, the Committee on Isotopes, studying this very thing. This year, in order to better define the

area of interest, the name was changed to the Committee on Radio-Pharmaceuticals. There are, however, at the present time a number of short-term, one month or less, training programs available to pharmacists. These include the several courses offered as a cooperative venture by the Greater Philadelphia Society of Hospital Pharmacists and The Philadelphia College of Pharmacy and Science, in Philadelphia, Pennsylvania; the various courses in Radiological Health offered by the Division of Radiological Health, U. S. Public Health Service, at the Robert A. Taft Sanitary Engineering Center in Cincinnati, Ohio; the course in Radioisotope Techniques given by the Oak Ridge Institute of Nuclear Studies in Oak Ridge, Tennessee; and there are several others. Many colleges and universities throughout the country offer courses at the graduate level, some at night and on Saturdays; many of these same institutions currently list full-time programs which lead to graduate degrees in several fields of interest.

Beneficial Effects

There is one other thought that I would like to leave with you today; and this is perhaps as important as any philosophical consideration facing the health professions at the present time. There has been evidenced in the last few years literally a deluge of articles appearing in both the professional and the lay information media concerning only the detrimental effects of nuclear energy—attributed to such things as nuclear weapons testing and nuclear power facilities. In addition, there have been a number of programs in the medium of television recently, some completely fictitious, others partly documentary in

View of a portion of the Radiopharmaceutical Service Laboratory at the Clinical Center, National Institutes of Health, Bethesda, Maryland



Assays are frequently done to determine the activity of a sample by using an electroscope which is placed at a measured distance from the radioactive material. Time, distance and rate of discharge of the electroscope are factors pertinent to determining activity of the sample

UNIVERSITY OF CHICAGO CLINICS PHOTO

nature. All of them considered the somewhat horrifying effects of exposure to ionizing radiation. I am sure that the use of so-called "scare journalism" is familiar to all of us. There exists an acute need for some positive reporting in these areas. All too little has been publicized concerning the tremendous benefits which can accrue from nuclear energy. When these benefits concern the health of individuals and of the nation, as is the case with the medical use of radioisotopes, the health professions have an obligation to elaborate on these benefits. Inherent in this obligation is the ability to discuss such matters with professional people and the lay public alike. Obviously, one cannot discuss anything intelligently unless one knows something about it. Therefore, it behooves all of us in the profession of pharmacy to learn as much as possible about the field of nuclear medicine. Whether or not we are directly responsible for radiopharmaceutical procedures, we all have the infinitely deeper responsibility of maintaining a sense of balance in the controversies regarding nuclear energy, its benefits, and its liabilities. Once this balance is established, we can fulfill this responsibility with factual and reasonable publicity wherever the need exists.

The time is fast approaching when the profession of pharmacy and, more specifically, the specialty of hospital pharmacy, must give serious consideration to determine the ways in which pharmacy can contribute to the over-all radiopharmaceutical program in this country. That we can contribute is obvious; that we should want to contribute is mandatory. Someone once pointed out that medicine, over the years, has advanced in almost direct proportion to the scope of the tools available. The invention of the microscope made possible the field of bacteriology; newer chemical and microbiological methods resulted in a whole host of valuable therapeutic agents. There is not the slightest doubt that the development and availability of radiopharmaceutical products will rank with any of these in the advancement of medicine.

Yes, nuclear energy is here to stay. And, happily, nuclear medicine is one by-product of this amazing technology which can only bring good to all of mankind.

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Suggested Criteria for PROPER LABELING OF SOLUTIONS REQUIRING RECONSTITUTION

by PHILIP R. HUGILL *and* MILTON W. SKOLAUT

► PHARMACEUTICAL PRODUCTS REQUIRING RECONSTITUTION in hospital use generally present problems due to lack of label information. The majority of these products are injectables, usually multiple dose vials. Every label examined met all label requirements as required by the Federal Food, Drug and Cosmetic Act as amended,[1] but each lacked essential information. Additional pertinent information should be included on each label for patient safety and to assure full drug potency.

To establish the need for additional information on some drug preparations, a group of 30 items, requiring reconstitution before use, was selected at random from the Pharmacy stock. Several label criteria necessary for proper use of the medication were examined. The chart lists these criteria and the findings.

Lot Numbers

As noted in the chart, some items have no lot number on the outside overwrap package. This proves troublesome to the pharmacist on those few occasions when a manufacturer will recall a specific drug lot. Packages must then be opened to verify the lot number.

Expiration Dates

A few items have no expiration date on the vial label. Nurses often take vials from the outer package for storage on the nursing unit, thereby discarding the expiration date and the package literature. True, the lot number is still on the vial and can be traced to yield the expiration date—but, for practical purposes, the expiration date has been lost. To a non-pharmacist, the very fact that the product has an expiration date is lost completely.

Stability After Reconstitution

Eleven of the 30 items had no information on the vial regarding stability after reconstitution. The information listed usually included "store in a refrigerator" and expiration date of the unreconstituted preparation. These 11 packages are not intended for multiple dose usage, since they contain no more medication than would be ordered for one treatment. However, this does not allow for the smaller pediatric doses, or those instances where medication is reconstituted but not administered. Even if the package is designed for single immediate use, there should never be any doubt, under any foreseeable circumstance, of its potency after reconstitution. These vials should bear a legend similar to "discard if not used immediately after reconstitution."

One product leaflet (Diamox, 500 mg.) advises that the vial is intended for two doses but contains no information as to the stability of the reconstituted product. It was noted that convenient information on how to prepare the medication for use was lacking. Information should be provided as to the quantity of diluent to be added to prepare a standard concentration of drug.

To reconstitute one product (Diuril, 500 mg.), the nurse or physician is required to read no less than 417 lines of text to discover the necessary information buried within the literature. Nowhere else on the vial or package is information given as to the correct diluent or to the fact that the unused portion should be dis-

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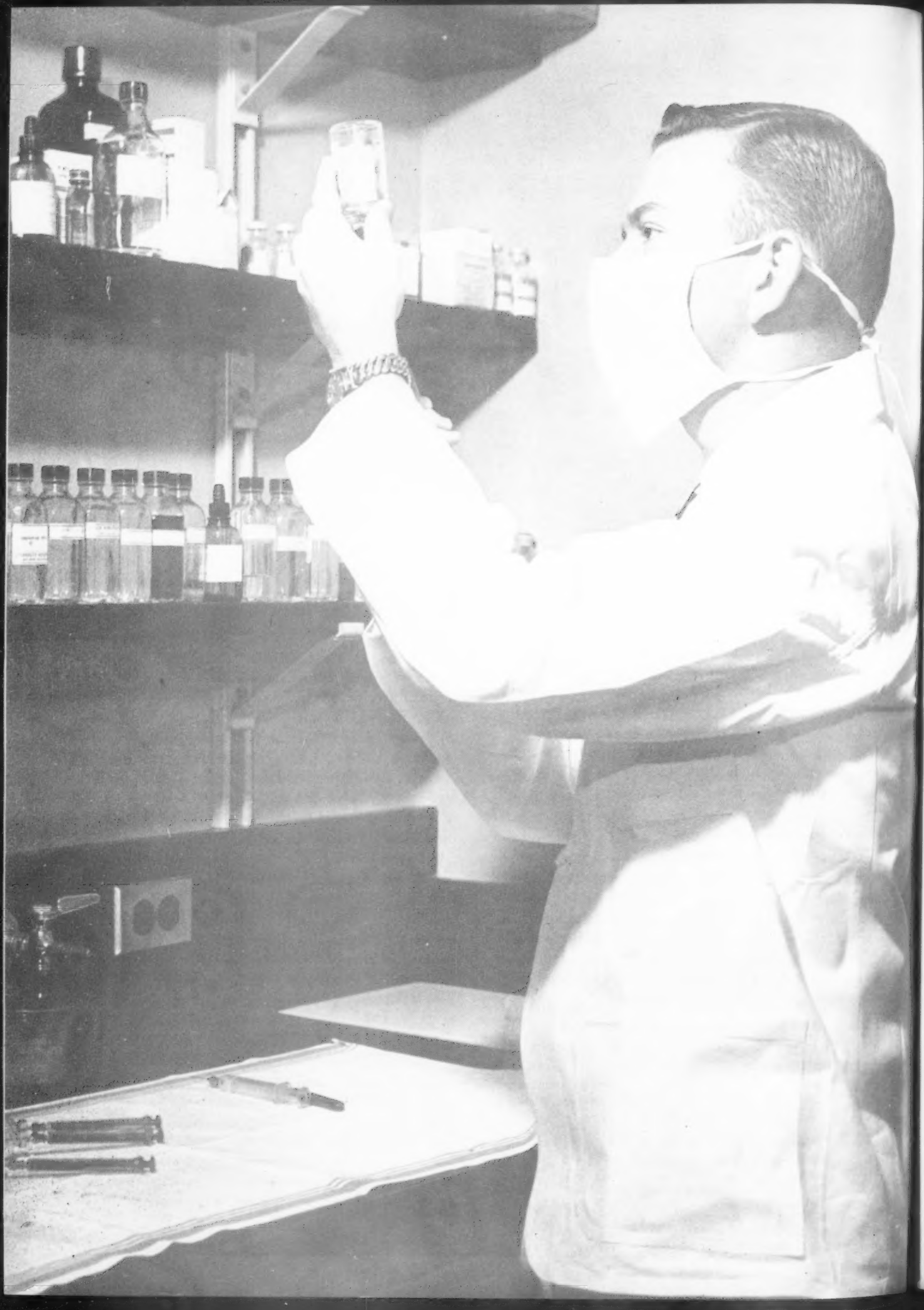
1. General Regulations for the enforcement of the Federal Food, Drug and Cosmetic Act, Title 21, Part 1.



Product and Manufacturer	Essential Label Information on Drugs Requiring Reconstitution						
	A	B	C	D	E	F	G
Mycostatin for Suspension, 100,000 units/ml., Squibb	x	x	x	x	x	–	0
Achromycin for Oral Suspension, 0.25 Gm., Lederle	x	x	x	x	x	x	0
Tryptar, 125,000 Armour units, Armour	–	0	x	–	x	x	0
Novobiocin (Cathomycin) Sodium, Lyovac, 0.5 Gm., Merck Sharp and Dohme	x	x	x	x	x	–	0
Erythromycin Lactobionate, 0.3 Gm., Abbott	x	x	x	x	x	x	0
Folbesyn vitamins, Lederle	–	x	x	–	0	x	–
Solu-B, Upjohn	–	0	x	–	0	0	0
Pro-Banthine, 30 mg., Searle	–	0	x	–	0	0	0
Solu-Cortef, Mix-O-Vial, 100 mg., Upjohn	x	x	x	x	0	x	0
Premarin I.V., 20 mg., Ayerst	–	x	x	–	0	x	0
Fungizone for Infusion, 50 mg., Squibb	x	x	x	x	0	x	0
Spontin, 0.5 Gm., Abbott	x	x	x	x	0	x	0
Varidase with Jelly, Lederle	x	x	x	x	x	x	x
Albamycin Mix-O-Vial, 0.3 Gm., Upjohn	x	x	x	x	0	x	0
Protamine Sulfate, 50 mg., Upjohn	–	0	x	–	0	x	0
Mycifradin Sulfate, 0.5 Gm., Upjohn	x	x	x	x	0	x	0
Polymyxin B Sulfate, 50,000 units, Pfizer	x	x	x	0	0	x	0
Corticotropin Injection I.V., 40 units, Upjohn	–	0	x	–	0	0	0
Aureomycin I.V., 0.5 Gm., Lederle	x	x	x	x	0	0	0
Vancocin I.V., 0.5 Gm., Lilly	x	x	x	x	0	x	0
Diuril Lyovac, 0.5 Gm., Merck Sharp and Dohme	–	x	x	–	0	x	0
Diamox, 0.5 Gm., Lederle	–	x	x	–	0	0	0
Tetracyn I.V., 0.5 Gm., Pfizer	x	x	x	x	0	0	0
Achromycin I.V., 100 mg., Lederle	x	x	x	x	0	x	0
Achromycin I.M., 0.25 Gm., Lederle	x	x	x	x	0	x	0
Combistrep, 1 Gram, Pfizer	x	x	x	0	0	0	0
Chloromycetin Succinate, 1 Gm. Steri-vial, Parke, Davis	x	x	x	x	x	x	x
Chloromycetin I.M., 1 Gm., Parke, Davis	x	x	x	0	0	x	0
Penicillin G Potassium Crystalline, Buffered, 500,000 units, Pfizer	x	x	x	0	0	x	0
Penicillin G Potassium Crystalline, 5,000,000 units, Lilly	x	x	x	x	x	x	0

A= Expiration date on outside carton
B= Lot number on outside carton
C= Lot number on immediate package
D= Expiration date on immediate package
E= Days or hours of shelf life after reconstitution on immediate package
F= Days or hours of shelf life after reconstitution provided in the package literature
G= Blank spaces provided on immediate package label for reconstitution date, reconstituted life, and concentration

x= yes
0= no
–= not applicable

carded after 24 hours. Should not this important information be placed on the vial or displayed in boldface type on a specific portion of the literature?

Only two of the 30 items surveyed had expiration dates on the vial, when it was applicable, with space provided by the manufacturer for reconstitution date and reconstituted strength. One of these two items (Chloromycetin succinate, injectable) was packaged in a vial with label space equal to or less than that of 70 percent of the items surveyed. This indicates that label copy can usually be adjusted to include this needed information.

At the Clinical Center Pharmacy, N.I.H., a series of pressure-sensitive labels has been prepared to be affixed to reconstituted vials. The general format is as follows:

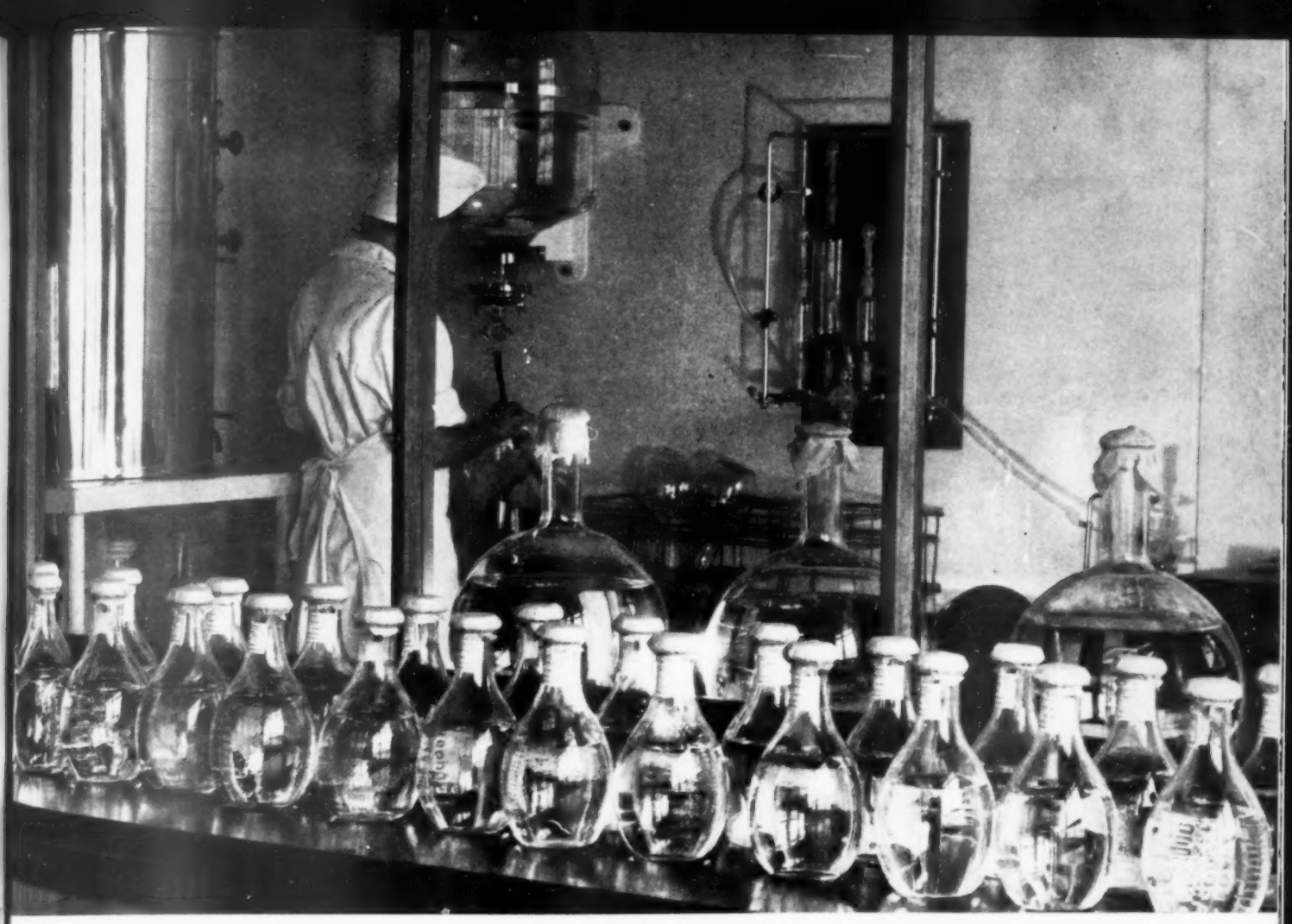
EXPIRATION DATE:
RECONSTITUTED:
DISCARD:
STRENGTH:

The first item, "expiration date," is listed for those items that have this information only on the outside package. The other three items are completed when the solution is prepared.

It is suggested that the pharmaceutical industry reexamine its respective label policies to meet hospital and patient safety requirements, in addition to the Federal Food, Drug and Cosmetic Label requirements.

HOSPITAL PHARMACY IN PORTUGAL

A separate sterile area is devoted to the preparation of ampuls and vials



Large volume injections are prepared using the Fenwal system

by ALUISIO MARQUES LEAL

► ONE OF THE APOTHECARIES OF THE court of King D. Manuel I (XVth century) was the first pharmacist known for his activity in the Hospital de Todos os Santos—the most important of old Lisbon and the earliest of its civil hospitals. The first nomination for the apothecary of Coimbra University—whose functions were generally different from those of the Royal hospital pharmacists of the same city—was made by King D. João III (XVth century).

It was also a pharmacist of the court who was first appointed director of the Royal Navy Hospital Pharmacy in the eighteenth century. Army hospital pharmacy has a long tradition in Portugal and retains today its great professional prestige. It has its origins in the eighteenth century also when King D. José I nominated the first pharmacist of the Court Army Hospital Pharmacy.

In Portugal, at present, the main hospital pharmacies are those of the state hospitals, those of the Army and Navy, those of the University Hospitals of Lisbon, Oporto and Coimbra which are attached to the medical schools although under the control of a Health State Department, and certain civil hospitals such as the Tuberculosis National Assistance Hospital, the Cancer Institute and the Neuro-Psychiatric Hospital, the latter three being located in Lisbon. In addition, there are several small pharmacies in some of the hospitals of villiages and towns.

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When the first principles of pharmaceutical instruction were adopted in the eighteenth century, two years of practice were required in the Dispensary of the University Hospital. The present pharmacy services of the great University Hospitals of Lisbon, Oporto and Coimbra have their origin in this beginning. However, in 1918, with the rise of autonomous schools of pharmacy, this obligatory practice in hospitals disappeared. It is probable that hospital practice will again be required when contemplated changes are made in the educational program for Portuguese pharmacists.

In preparing a short summary of hospital pharmacy in Portugal it is important to mention the role played by the Sociedade Farmacêutica Lusitana, a scientific organization founded in 1835. The first headquarters of this organization were in St. Joseph's Hospital and many of its first members and directors were hospital pharmacists. Foremost among these was Emílio Fragoso, author of an outstanding formulary, who directed the Civil Lisbon Hospital Pharmacy Services with great competence and merit.

Organization and Responsibilities

As in many other countries, the hospital pharmacy services of Portugal supervise the procurement, checking, preparation, storage and distribution of medicinals. In addition, the pharmacy also is responsible for reagents and culture media for the clinical laboratories and for the chemical products and contrast media employed by the radiology services. Medicinal gauzes and other dressings are in some cases the responsibility of the pharmacy. Also, when there is no central supply department in the hospital, the pharmacy sterilizes materials for surgical dressings, clothing, etc., and prepares anticoagulant solutions for the collection of blood.

As a rule, in Portugal, the hospital pharmacist has no administrative responsibility in the clinical analyses laboratories. These are usually under the supervision of specialized physicians who also perform many of the analyses. There are, however, pharmacists working as analysists or assistants in some of these departments. As an exception to this general rule, a professor of pharmacy is Director of the Clinical Analyses Laboratory of the Tuberculosis National Assistance.

In the main hospitals, procurement of drugs and medicines is done by the purchasing department on a monthly or quarterly basis using a system of competitive bidding and following the specifications established by the director of pharmacy services.

Although the fixtures and equipment of most hospital pharmacies are not up-to-date, for most of them are old and those of the new Lisbon University Hospital were outgrown soon after being built, we may say that the pharmaceutical service rendered is good.

The control laboratories of the pharmacies are equipped with apparatus for the chemical-physical analyses of drugs. Here, the purity of purchased drugs is verified and medicinals prepared in the hospital pharmacy are analyzed. The latter include such preparations as tinctures, extracts, tablets, injectable products, etc. Upon request of the administration, these laboratories sometimes analyze foods and perform toxicological studies as requested by the emergency service in case of serious poisoning. It may also help the Clinical Analyses Service in the preparation or purification of rare or difficult-to-obtain reagents and in the determination of medicinals in biological fluids.

Manufacturing

The manufacturing sections of the chief Portuguese hospital pharmacies generally consist of five main units, some of which may be divided into several rooms. These units are for:

1. Tablets, powders, and similar products
2. Injectable products in ampuls or vials
3. Liquid preparations such as syrups, solutions, and emulsions
4. Solid galenical preparations such as ointments and suppositories
5. Water distillation and sterilization.

Most of the medicines supplied to the clinical services are usually prepared in one of these units of the pharmacy. The preparations include official products, formulary preparations, and many new specialized medicines when the raw materials may be purchased at a low price. Several hospital pharmacies have, or will have aseptic rooms for the preparation of penicillin and streptomycin injections.

Other units of the hospital pharmacy, although differing from hospital to hospital, usually include the following:

1. Storeroom for flammable and corrosive liquids
2. Storeroom for solid drugs and reagents
3. Storeroom for galenical hospital preparations
4. Storeroom for specialties and narcotics
5. Storeroom for empty containers such as bottles, ampuls, and capsules
6. Receiving and delivery room
7. Director's office and library
8. Accounting office for departmental records.

Distribution

Each morning the nursing and clinic units requisition their needed supply of drugs from the pharmacy. The drug baskets are brought to the pharmacy by attendants who bring the necessary requisitions and clean, empty containers. In the afternoon the filled orders are delivered to the proper units.

Hospital pharmacies in Portugal do not sell medicines to the public. The only exceptions to this rule are the Army Central Hospital and the Navy Hospital Pharmacy. Hospital pharmacies supply medicine to inpatients. In some cases the drugs are supplied free

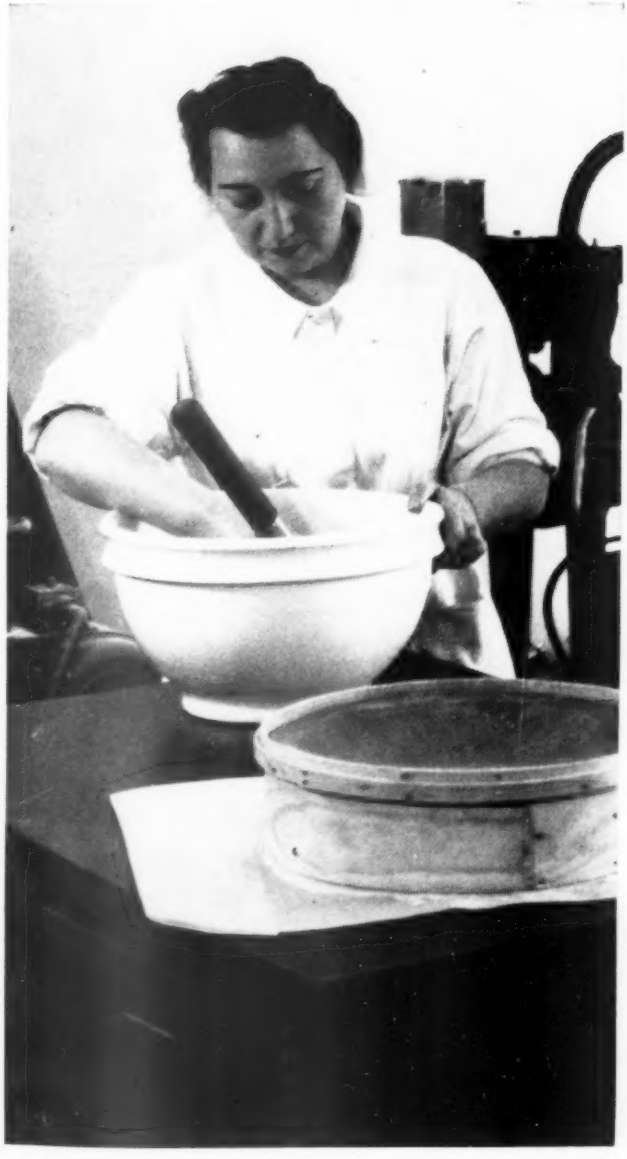
while in others a charge is made. Drugs are always supplied without charge to indigent outpatients and to those who are treated in the emergency service of the hospital. Because of this, hospital pharmacies are required to maintain a record of the purchases and supply of all drugs, including their cost prices. This record is sent periodically to the administrator and becomes a part of the hospital's permanent accounting record.

Staffing Patterns

There is no unified legislation regarding the staffing of hospital pharmacies. Each department usually consists of the managing pharmacist, staff pharmacists, technical auxiliary helpers, and cleaning staff.

In Portugal there are two university courses for the education of pharmacists. Of the two courses, one is three years and the other is five years in duration, the latter resulting in an academic degree similar to that of the other liberal professions. Graduates of the general course hold posts in some of the less important hospitals. However, in the main hospitals only the chemists-pharmacists are admitted. In these hospitals there are several categories of pharmacists, usually a chief pharmacist and one or more assistants. However, in the larger general hospitals, civilian and those of the universities, there is a director of pharmacy service, chief pharmacist and assistants.

A view of the tablet department at the University Hospital of Lisbon



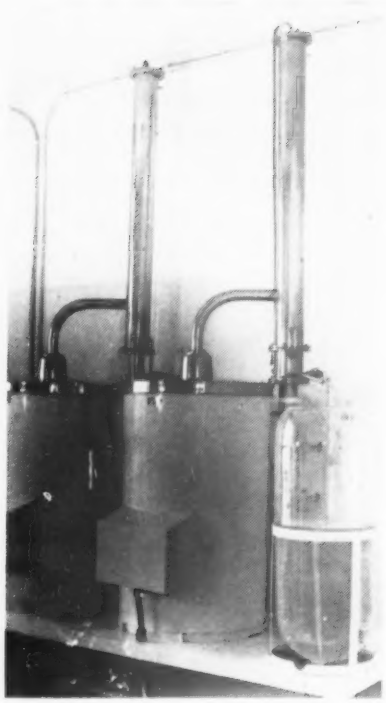
Internships

Hospital pharmacy internships, similar to those of France, were established only a short time ago, in 1953, with the last reorganization of the Lisbon Civil Hospitals. This system is still practically in its infancy and it will be some years before enough interns are trained to permit selection of new assistants from among the hospital pharmacy interns.

Competitive examinations for the post of hospital pharmacist assistant, although not uniform, are generally difficult and consist of written, practical, and oral examinations which demand considerable scientific knowledge and technical skills. The organization and nature of the examinations are very similar to those given to applicants for the internship in French hospitals, except for those who want to specialize in clinical analyses. The jury giving the examination is generally composed of the head pharmacists and sometimes includes professors of pharmacy and medicine, the latter more often as pharmacologists.

The technical auxiliary staff consists of pharmacy helpers who assist in the preparation and analysis of medicines and others who deliver medication, clean glass ware, seal ampuls, etc. These helpers are usually employed after having passed rather simple practical tests. The number of helpers usually exceeds the number of pharmacists in a hospital pharmacy.

Salaries of Portuguese hospital pharmacists, while



A Kottermann apparatus for producing double distilled water

The sterilization room, snowing two autoclaves

not uniform, are usually much lower than those of their foreign colleagues, excepting the Italians whose salaries are approximately equivalent. Pharmacists of the Army and Navy hospitals receive larger salaries than those in civil hospitals. Since there are many pharmacists in civil hospitals with equal education to that of the military pharmacists, and equal to that of other professionals with university courses, it is hoped that the government will soon justly solve the existing imbalance. In general, Portuguese hospital pharmacists have a salary scale which is about one-half of that received by the Swiss or French hospital pharmacists.

Professional and Administrative Relationships

While Portuguese hospital pharmacists are professionally independent, they are subject to the administrative discipline of the hospital and are directly responsible to the hospital administrator. In large general hospitals the director of pharmacy service is a permanent member of the hospital's Technical Council. This Council is composed of representatives of the various clinical departments, diagnostic auxiliary services, administration and nursing, and is presided over by the Clinical Director.

Only the chief pharmacist may select the raw materials used for the manufacture of medicinal preparations and it is he who decides the techniques to be employed in their preparation. In this way, the chief pharmacists become, in effect, counselors for the administrator and purchasing agent.

Hospital pharmacists play an important role in the development of the several formularies used in various Portuguese hospitals. In these formularies are included the medicinal agents available from which the physician may make his choice. In the Lisbon civil hospitals there is a permanent formulary committee and in St. Mary's Hospital there is a Pharmacy and Therapeutics Committee composed of pharmacists and physicians. This Committee is similar to those existing in American hospitals and is responsible for making revisions in the formulary and acting as a general advisory group on matters related to drugs for hospital use.

As a rule, only one brand of a specialized medicine is stocked in the principal Portuguese hospitals. Physicians may obtain other brands only by permission of the clinical director of the hospital. This rule allows the hospital to control its budget for drugs and still permits the clinical director, in collaboration with the chief pharmacist, to evaluate all requests for other drugs. In some hospitals, however, there is no limitation on either the brand or type or quantity of medication which may be prescribed.

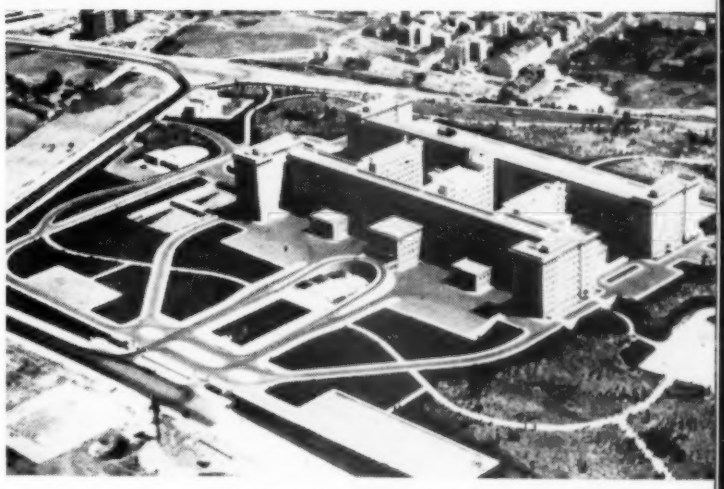
Research and Teaching

As in most other countries, most of the research papers published by the Portuguese pharmaceutical

journals are the work of professors and assistants of schools of pharmacy. However, since the beginning of the century several hospital pharmacists, including those of the Army and Navy have contributed research papers to medical, pharmaceutical and hospital journals. In the main, these papers have dealt with pharmaceutical analysis and with various aspects of pharmaceutical technology. These research papers have been prepared in spite of the shortage of personnel to carry out the routine work of the pharmacy and their preparation has been possible only because of the splendid cooperation of students who have volunteered to assist in the pharmacy.

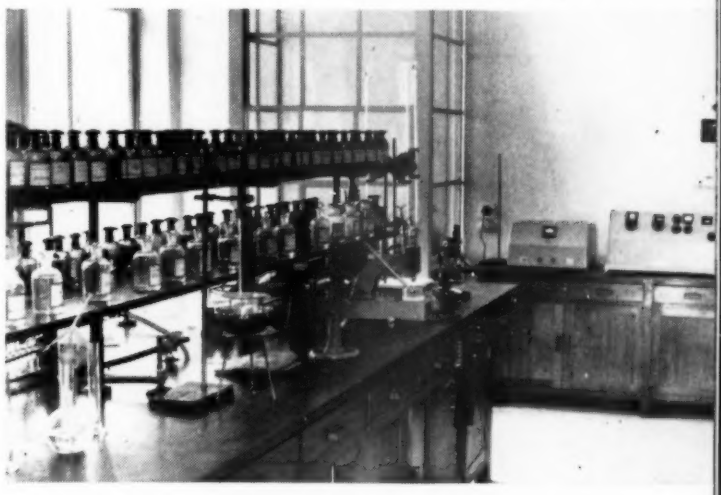
During recent years a section devoted to hospital pharmacy has been contributed to the journal *Portuguese Hospitals* by the hospital pharmacists of Lisbon.

In general, hospital pharmacists in Portugal do little teaching of nurses, medical students, or others. Exceptions to this are the hospital pharmacists of the Army and Navy who cooperate in the presentation of courses for hospital personnel; and this year, for the first time, the chief pharmacist of the Cancer Hospital was appointed Instructor in Pharmacology and Therapeutics in its School of Nursing. In addition, the Pharmacy Department of St. Mary's Hospital cooperates with the medical and nursing schools to instruct students in some of the fundamental processes used in the preparation of medicinals.



University Hospital (St. Mary's) of Lisbon

A view of the Control Laboratory at the University Hospital of Lisbon



Professional Organizations

Since there are now less than 100 hospital pharmacists in Portugal, there is no separate professional organization for hospital pharmacists. Rather, all hospital pharmacists are required to be a member of the Pharmacists' National Syndicate. This association now occupies the quarters of the old Luso-Pharmaceutic Society. It maintains a vast pharmaceutical library and publishes the *Portuguese Pharmacy Journal*, a professional and scientific publication which is a continuation of the *Luso Pharmacy Society Journal*. The editorial committee is composed of three hospital pharmacists, one of whom is also President of the Board of Directors of the Pharmacists' National Syndicate. Two hospital pharmacists are members of the Revision Committee of the *Portuguese Pharmacopoeia*.

Although hospital pharmacists do not have a separate organization, they do hold monthly meetings at which they discuss scientific and professional subjects of special interest to hospital pharmacy practice.

While there is no legal restriction preventing hospital pharmacists from engaging in other professional activities, they cannot, however, be the technical director of a private pharmacy. Most hospital pharmacists are required to work in the hospital on a full-time basis and only the most distinguished pharmacists have an opportunity to do consulting work for the pharmaceutical industry.

TEXAS MEDICAL CENTER

. . . its history, services and hospital pharmacy

By ADELA SCHNEIDER *and* PAUL D. WILBURN

► THIS YEAR 1959 MARKS THE 20TH ANNIVERSARY of the death of a great Texas philanthropist, Monroe D. Anderson, who left his entire 20 million dollar estate to be set up as a permanent foundation which was to have among its many humanitarian purposes "the promotion of health, science, education, advancement and diffusion of knowledge and understanding among people."

It was a fortunate foundation from the beginning in that it was directed by a board that was inspired to carry out a vision long held by both physicians and laymen of Houston—that of the establishment of a medical center to provide the citizens of the entire state of Texas with the best possible facilities for prevention, treatment and rehabilitation.

The Medical Center that grew out of this dream is indeed a unique one. It is not a single-institution but a multiple-institution enterprise. Its governing body is comprised of many boards totaling some 220 members instead of the traditional board of nine that usually constitutes a board of regents or trustees. The Medical Center comprises approximately 160 acres and today has more than a dozen institutions, the buildings alone representing an investment of over 56 million dollars. With the buildings now on the drawing board and with the investment in sewers, lights, streets, etc., the sum total of investment will be over 100 million dollars upon completion of the planned buildings, and there will be approximately 3,000 hospital beds.

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Initial Steps

The initial step toward the development of the proposed Texas Medical Center was taken when the Texas Legislature in 1941 authorized the establishment of a cancer hospital as a branch of the University of Texas, and the M. D. Anderson Foundation induced the Board of Regents to locate this institution in Houston, in spite of the fact that the University itself is in Austin and its medical branch in Galveston.

When, at the end of 1943, Baylor University College of Medicine moved to Houston after 30 years in Dallas and the Texas Dental College in Houston was officially made a branch of the University of Texas, the Foundation set further steps in motion toward the realization of a medical center by promising large tracts of land plus financial help to these institutions. It ultimately purchased 130 acres adjoining the 20-acre George Hermann estate upon which for many years the original Hermann Hospital had stood alone with its nurses' home. Deed to the 130 acres was officially presented to the citizens of Texas on February 28, 1946.

At the conclusion of World War II Baylor Medical College, with funds from the Anderson Foundation and through the generosity of Houston oilman and philanthropist H. R. Cullen and wife, built its new home in a commanding position on the 130 acres and was

ready for occupancy by the fall of 1947—the first building in the new medical center.

Following the opening of the new Hermann Hospital in 1949, there sprang up in quick succession a new Methodist Hospital, the Arabia Temple Crippled Children's Clinic, Texas Children's Hospital, the University of Texas M.D. Anderson Hospital and Tumor Clinic, and St. Luke's Episcopal Hospital. The Jesse Jones Medical Library was opened in 1954, and the Texas Institute for Rehabilitation and Research in 1958.

In addition to the expansions mentioned, the following are in the planning stages or are now being built:

1. The Houston Speech and Hearing Center
2. The Houston State Psychiatric Institute
3. A branch of the Texas Women's College of Nursing
4. A Commons Building for Nurses, by the Good Samaritan Club
5. An Institute of Religion Building (non-denominational) to offer training and degrees to chaplains.
6. The Jesse Jones Research Building
7. Anderson Basic Research Building
8. Jewish Medical Research Institute
9. A Lutheran General Hospital with 250 beds
10. A City-County Hospital for the acutely ill, with 350 beds.

A Cardiovascular Institute and an Institute of Life Chemistry are being planned for future building.

Hospital Pharmacy

And now, about hospital pharmacy in the Medical Center. As can be expected, the pharmacy service is in keeping with the finest traditions of the Center, and the hospital pharmacists are among the most professional in the Houston Area. Presently there are 20 pharmacists in the Center, concentrated in four hospitals, as compared with the 2 that were at the original Hermann Hospital at the time the idea of the Medical Center was conceived.

Increase in the number of hospital pharmacists in the Houston area, enhanced not only by the establishment of the Medical Center hospitals but also by the location of the Veterans Administration Hospital in the shadow of the Medical Center, stimulated a need for organization and provided the incentive for the founding of the Houston Area Society of Hospital Pharmacists in 1955.

Alert pharmaceutical companies who saw advantages of assigning medical service representatives strictly to the Medical Center hospitals and the professional buildings nearby, selected representatives with an intensive interest in and a high regard for hospital pharmacy who have contributed valued associate membership to the Houston Area chapter. Adding prestige, also, to the associate membership are pharmacy school faculty members, for two of the three colleges of pharmacy in Texas are in close proximity to the Medical Center.

Future Potentials

As hospital facilities are expanded, there will of course be a proportionate gain in the number of hospital pharmacists serving the area. The future promises many potentials as services grow. Hospital pharmacy internships with versatile training in a variety of hospitals all concentrated in a small area, a medical center formulary, perhaps, a hospital pharmacy newsletter with the pharmacy staffs of all the hospitals as editors, one-day institutes and other teaching programs as well as lecture-series for hospital pharmacists by faculty members of nearby medical, dental and pharmacy colleges, visitation programs for pharmacy college students, as well as development of special research through joint effort.

It must be confessed that originally, in the energetic eagerness to put something on the 130 acres, buildings were designed before staffs were employed and department heads named. In consequence, with no pharmacists to help with plans in some of the hospitals, the pharmacies left much to be desired. Main blooper was allottment of too little space; hence after occupancy, nearby areas had to be allotted to the pharmacies with the result that the departments sadly lack the finish a well-planned hospital pharmacy by the U. S. Public Health Service, for instance, would have. Generally, the pharmacies are still deficient in adequate working area.

To compensate in part, if that is possible, the Houston Area Society of Hospital Pharmacists in October 1958 passed a resolution to contact all groups in the Houston Area who are planning hospitals, in the Medical Center or elsewhere, offering them assistance in designing the pharmacies in the buildings being considered. It is the hope of the special committee working on this project that results will be achieved which will reflect the mutual goals in mind.

Private Enterprise and Public Service

In conclusion, the interesting fact should be pointed out that as other professional buildings arose along Fannin Street across from the Medical Center, privately-owned pharmacies and prescription shops grew along with them. Now there are ultra-modern drug stores in the Hermann Professional Building, the Medical Towers Building, and the Diagnostic Clinic, while two independent prescription shops flourish alongside of them—all attesting to the fact that even in a specially-designed hospital center, hospital pharmacy need not be a competitor to the other segments of pharmacy that specialize in prescription business.

physico-chemical properties and biological activities of CYTOTOXIC AGENTS & DRUGS

by JOHN AUTIAN

Part One

► IN THE PAST, THE SCHOOLS OF PHARMACY HAVE presented pharmaceutical or medicinal chemistry solely based upon the relationship of the chemical structure to its biological activity. This in part was due to the tens of thousands of organic compounds already biologically tested in which structural similarities could be readily detected. Unfortunately, the theory or concept was never quite complete and even useless in comparing certain similar compounds which produced quite varied biological responses. Today in many of the schools, with the help of the information from the biochemist, physical chemist, bio-physicist and other biological scientists, certain physico-chemical properties are being related to the biological activity of drugs and chemical agents. In a number of in-

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Table I. Molar Concentration of Narcotic Agent to Cause Paralysis in Tadpoles[4]

	Narcotic conc. for tadpoles mol./water	Distrib. coeff. olive oil/water	Narcotic conc. calculated mol./lipoid
Ethyl Alcohol	0.4	0.03	0.0120
Propyl alcohol	0.11	0.13	0.0140
Butyl alcohol	0.13	0.18	0.0230
Ethylurethane	0.04	0.03	0.0012
Valeramide	0.05	0.07	0.0035
Ether	0.024	2.4	0.0576
Benzamide	0.005	0.44	0.0022
Salicylamide	0.002	14	0.0028
Carbon disulfide	0.0005	50	0.0250
Phenylurethane	0.0006	150	0.0900
Menthol	0.0001	250	0.0250
Thymol	0.000055	600	0.0330
Average	.....	.....	0.0241

stances, this approach more adequately explains drug activity than the usual structure-activity relationship.

The information presented in this paper is intended to review some of the knowledge existing upon the subject of physico-chemical properties and biological activities of general cytotoxic agents and drugs. There has been no attempt to review all of this subject matter with scrupulous thoroughness. In fact, certain aspects of the subject have not been included while just fleeting mention is made of others. For the busy hospital pharmacist, this discussion is intended as an introduction to the field. Those pharmacists desiring fuller treatment of the subject are encouraged to seek the literature included in the references.

Specific and Non-Specific Drugs

In general, drugs may be classified into two groups, (a) structurally specific and (b) structurally non-specific. The structurally specific drugs are those substances which, because of their chemical and physical configurations, can discriminate and impinge upon the receptor site responsible for a certain biological activity. A slight alteration in the structure of the drug may sharply decrease or abolish the original activity. The majority of drugs fall under this classification. There are, however, certain groups of pharmacologically similar drugs, such as the narcotics, some insecticides, etc., which may be classified as structurally non-specific, for they evoke a similar overall biological response although probably by diverse biochemical mechanisms. They need not be related structurally to other agents having similar effects; their activity may be correlated with several of their physical properties. The most successful application of relating physical properties to biological effects has been in the series of narcotics and general cytotoxic agents.

Meyer-Overton Theory

At the beginning of the century, Overton[1] and Meyer[2] postulated that narcosis was related to lipid solubility of the drug. They visioned that the drug has a physical effect upon the cell protoplasma and that as the external concentration of drug was increased the internal concentration (in cell) would reach a level causing narcosis. Furthermore, this internal concentration of the drug would be approximately the same for all the narcotics employed.

K. H. Meyer and Hemmi[3] surmised that, since the narcotic effect was a direct consequence of lipid solubility in the cell, the concentration in the cell lipid could be calculated if two facts were known. These were (a) the minimum molar concentration of drug in the external medium (air or water) to cause equi-narcosis in the test organism and (b) the distribution coefficient of the drug between the oil/water or air phase. The narcotic concentration in the lipid could then be calculated by multiplying the molar concentration of the narcotic in the external medium by the distribution coefficient between the oil and water. Many oily substances have been employed as models of the cell lipid. Even though it was known that some of these oils were not a true representation of cell lipid, surprisingly good results were obtained when the distribution coefficients obtained with these oils were used in calculating the drug concentration in the cell lipid.[4] In actual practice, however, there was no way of knowing if this really was the lipid concentration in the living protoplasm. The somewhat misleading assumption was strengthened by the work of Meyer and associates.[5] Table I depicts how the distribution coefficient, when multiplied by the equi-narcotic effect in tadpoles, will give results which will fall in a narrow range. It will be noticed that the narcotic concentration in water varies from 0.4 molar for ethyl alcohol to 0.000055 molar for thymol while the drug concentration in the lipid remains in a rather limited range. A number of objections have been made to this theory since the extent of drugs employed was relatively limited.[6,7] Others have objected to the theory on experimental grounds.[8]

Thermodynamic Activity

Ferguson[9] felt that a more accurate picture of the narcotic and toxic actions of unrelated chemically inert drugs could be portrayed by the application of thermodynamics. He surmised that an equilibrium existed between the drug concentration in the external medium and the cell protoplasm. For example, certain drugs produce a narcotic effect on organisms, and this action remains until the drug is removed from the external environment.

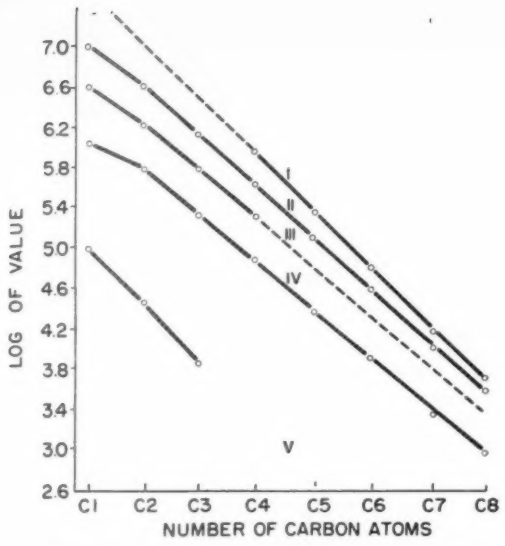

FIG.-1 PROPERTIES OF NORMAL PRIMARY ALCOHOLS *(9)*

I. SOLUBILITY (MOL. X 10^{-6}/LITRE)
II. TOXIC CONCENTRATION FOR B. TYPHOSUS (MOL. X 10^{-6}/LITRE)
III. CONCENTRATIONS REDUCING S.T. OF WATER TO 50 DYNES/CM (MOL. X 10^{-6}/LITRE)
IV. VAPOR PRESSURE AT 25° (MM. X 10^{-4})
V. PARTITION COEFICIENT BETWEEN WATER AND COTTON SEED OIL (X 10^{-3})

In certain homologous series, there is a decrease in equi-toxic or equi-narcotic concentration as the series is ascended. A graph comparing a number of physical properties and the toxic concentration of normal primary alcohols (Fig. 1) shows the close relationship between these physical properties and the toxic concentration and further establishes that for each physical property plotted, there exists a distribution between heterogeneous phases. Thus, solubility is the distribution of a solute between the pure solid or liquid and its saturated solution; vapor pressure is the distribution of a pure solid or liquid between its pure state and its vapor, and etc. Ferguson concludes that "since the molar toxic concentrations in a homologous series change on ascending the series not by equal steps but that instead their logarithms decrease by equal steps, it is to be concluded that they are largely determined by a distribution equilibrium between heterogeneous phases—the external circumambient phase where the concentration is measured and a biophase which is the primary seat of toxic action."

When chemically unrelated drugs exert narcotic and toxic activity reversibly, their activity is also ascribed to the "whole" molecule. If this hypothesis is valid, and there is ample evidence to support this contention, the drug concentration in the external phase is in equilibrium with the internal concentration in the cell or organism. It would then follow that the thermodynamic or chemical potential of the drug or agent would also be equal in both phases. To find the thermodynamic potential in the cell or organism, one would have to determine only the potential in the external phase, since both would have the same value.

Ferguson[9] used the partial molal free energy of the drug compared to a standard state as the thermodynamic potential. The thermodynamic relationship between partial molal free energy and concentration of the drug may be shown by the expression:

$$F = F_0 + RT \log a$$

where F is the partial molal free energy of the drug in one state, F_0 the partial molal free energy in the standard state, a, the concentration term expressed as "activity" of the drug in a gas or a solution, R and T the gas constant and absolute temperature respectively. For a specific drug or agent at a specified temperature and pressure, F_0 will be constant and "a" or activity will be a measure of the thermodynamic potential (partial molal free energy) and will have the same magnitude in both the external and internal phases of the cell or organism. These activities then can be employed as indices for narcotic and toxic effects when equi-narcotic or toxic doses are administered to a given organism.

The activity values may be approximated for volatile substances (applied as a vapor to the organism) by the use of the expression Pt/Ps where Pt is the partial pressure of the drug and Ps, the saturated vapor pressure of the drug at the temperature of the experiment; or for a drug of limited solubility in solutions, St/So where St is the molar concentration of the drug and So, its solubility.

The thermodynamic activities for a number of narcotic and toxic susbtances have been compared to the dose required to produce an equi-biological effect (narcosis or toxicity). Their values are listed in Table II. Ever though there is a 200 fold difference in concentration of nitrous oxide and chloroform

Table II. Isonarcotic Concentrations of Gases and Vapors for Mice at 37°[9]

SUBSTANCE	NARCOTIC CONC. % BY VOLUME	ACTIVITY Pt/Ps
Nitrous oxide	100	0.01
Acetylene	65	0.01
Methyl ether	12	0.02
Methyl chloride	14	0.01
Ethylene oxide	5.8	0.02
Ethyl chloride	5.0	0.02
Diethyl ether	3.4	0.03
Methylal	2.8	0.03
Ethyl bromide	1.9	0.02
Dimethylacetal	1.9	0.05
Diethylformal	1.0	0.07
Dichlorethylene	0.95	0.02
Carbon disulfide	1.1	0.02
Chloroform	0.5	0.01

Table III. The Activities of the Alcohols in Equi-Toxic Solutions for Various Toxic and Narcotic Actions[9]

	Inhibition of development of sea urchin eggs		Tadpole narcosis		Bactericidal concentration B. typhosus		Hemolysis of ox blood		Fumigation red spider	
Alcohol	Mol./L.	Activity	Mol./L.	Activity	Mol./L.	Activity	Mol./L.	Activity	Mol./L.	Activity
Methyl	0.719	0.019	0.57	0.014	10.8	0.33	7.34	0.22	0.00017	0.26
Ethyl	0.408	0.026	0.29	0.020	4.86	0.32	3.24	0.22	0.00010	0.32
Propyl	0.136	0.034	0.11	0.029	1.50	0.34	1.08	0.24	0.000047	0.42
Butyl	0.0454	0.043	0.038	0.038	0.45	0.37	0.318	0.27	0.000017	0.47
Amyl	0.0204	0.070	..	..	0.13	0.52	0.091	0.31	0.0000081	0.56
Hexyl	..	..	..	..	0.039	0.63	..	..	..	..
Heptyl	0.00172	0.112	..	..	0.012	0.74	0.012	0.77	..	..
Octyl	0.00051	0.113	..	..	0.0034	0.88	0.004	0.87	..	..

to produce equi-narcosis, the "activities" are the same. In fact, it is seen in the same table that the activities fall within a very narrow limit (0.01-0.07). The differences are believed to be due to the variance in chemical structure.

In a number of calculations of thermodynamic activities in homologous series, Ferguson noticed an increase, though small, of activities as the series was ascended. Table III shows these results for a number of related experiments.

The thermodynamic principle can be of value in determining if new compounds act by a physical (structurally non-specific) or chemical (structurally specific) process. The thermodynamic activities of the new drugs should be determined and these values should be compared to known thermodynamic activities of drugs acting through a physical means on specified organisms to elicit an equi-biological effect. If the thermodynamic activities of the new drugs fall within the limits of the activities of the known drugs, the action is probably due to a physical or more rightly physico-chemical (non-specific) mechanism.

Brink and Posternak[10] found that equi-narcotic effect for an equal thermodynamic activity was probably more general than expressed by Ferguson. For example, contrary to Ferguson's view of an increase of activity as a homologous series was ascended, the activity might remain constant or even decrease depending upon the test organism. An interesting observation was made by Posternak and Larrabee[10] on suppression by narcotic agents of transmission over synaptic and non-synaptic pathways of the stellate ganglion of the cat. They found that in a homologous series the thermodynamic activities remained relatively constant but increased (Ferguson effect) as the series was ascended for suppression of conduction over the non-synaptic pathways (see Table IV). Brink and Posternak[10] could not explain the reason for the two different effects but concluded that the cell structure was responsible for such anomalous behavior. They felt that "the molecular explanation of the changes in narcotic effectiveness is apparently to be sought in the molecular origin of changes in molecular cohesion of the pure narcotics. It seems probable that such narcotics produce their effect in regions of the cell into which they can fit, as much as they fit into their own pure liquid. If this is correct, then equal degrees of narcosis are caused by equal numbers of narcotic molecules in those portions of the cell in which the narcosis occurs."

Table IV. Reversible Suppression of Transmission of Nerve Impulses[10]

	Synaptic Pathways		Non-Synaptic Pathways	
Molecule	Narcotic Concentration mole/liter	*A x 10^2	Narcotic Concentration mole/liter	*A x 10^2
n-Methanol	2.250	6.4	1.000	2.8
n-Ethanol	0.478	3.2	0.240	1.6
n-Propanol	0.216	5.7	0.179	4.7
n-Butanol	0.048	4.6	0.048	4.6
n-Pentanol	0.0092	3.6	0.0166	6.4
2 Hexanol	0.00314	2.5	0.00668	5.3
2 Octanol	0.000382	4.1	0.00191	21.0
Chloroform	0.0044	6.3	0.0132	19.0
Ethyl ether	0.0336	4.2	0.096	12.0

*A - Thermodynamic Activity.

Van Der Waals' Constant

Wulf and Featherstone[11] found that another physico-chemical property, van der Waals' constants, could be applied to depict general anesthetic activities. For a real gas, the mathematical relationship of temperature and pressure on volume may be expressed by van der Waals' equation:

$$\left(P + \frac{a}{V^2}\right)(V-b) = RT$$

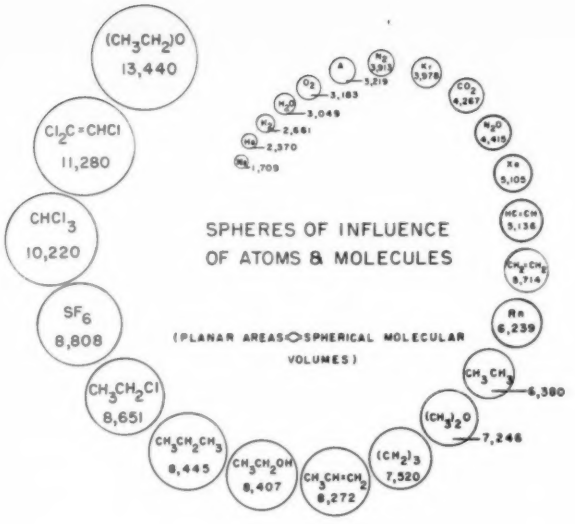

FIG.-2 SPHERES OF INFLUENCE OF ATOMS & MOLECULES (10)
(THE NUMERICAL VALUES ABOVE ARE VAN DER WAALS CONSTANT "b" X 10^2)

where P, V and T are pressure in atmosphere, volume in liters and absolute temperature respectively and R, the usual gas constant. In this equation, "a" is the term used to indicate the attractive force between gas molecules and "b," the effective volume of the molecules in one mole of gas. By arranging a number of substances according to their increasing magnitude of "a" and "b," a very close correlation with anesthetic potencies (increase of anesthetic activity with increase of constants) was found.

This relationship between the relative molecular volumes (van der Waals' constant "b") of a number of non-anesthetic and anesthetic agents, and anesthetic action is illustrated in Figure 2. Those substances having the smaller volumes do not possess activity, but as the volumes of the atoms or molecules increase greater activity is obtained. This relationship is consistent with the view that narcotic agents produce their effect because they can "fit" into chemical structures within cells controlling wakefulness.[10] In general then, it would seem that non-specific drugs behave as neutral molecules exerting a narcotic action on the organism of cells by some physico-chemical phenomenon. However, at the present time there is no way to predict from physico-chemical properties if a drug will act as a narcotic or non-narcotic agent; nor can these same properties describe the mechanism by which certain drugs depress the physiological activity of the cells or organisms under study.

Effect of Chain Length

As in narcosis, the toxic effect produced by a number of antiseptics such as the alcohols and phenols on bacterial cells, at least in the inital stages of toxicity, is also a reversible reaction between the antiseptic agent in the external environment of the cell and the drug in the cell. The irreversible effects causing death of the bacteria probably are attributable to secondary factors.

Schaffer and Tilley[12] studied the germicidal effects of a number of monohydric alcohols and phenols on *Bacillus typhosus* and *Staphylococcus aureus*. They found that in a homologous series of primary alcohols the antiseptic potency increased in nearly geometric progression as the series was ascended and there appears to be a constant ratio between each two successive homologs. This is true for all the alcohols except methanol. As the molecular weight for the alcohols increases, the antiseptic activity against each organism also increases, reaching a point of maximum activity and then decreases (cut off point) as the molecular weight increases. However, the maximum activity occurs at a lower point in the series for *B. typhosus* than for *S. aureus*. The difference in the behavior of one antimicrobial agent against various test organisms has been termed a "quasi-specific" effect. This type of relationship has also been seen for a number of other pharmacological effects,[13] such as hemolysis of red blood cells, toxicity of plants to certain organisms and the inhibition of sodium permeability into erythrocytes by alkyl carbamates.

In the study of alkyl derivatives of resorcinols, *n*-hexyl resorcinol had the highest phenol coefficient in the homologous series. Figure 3 depicts a comparison

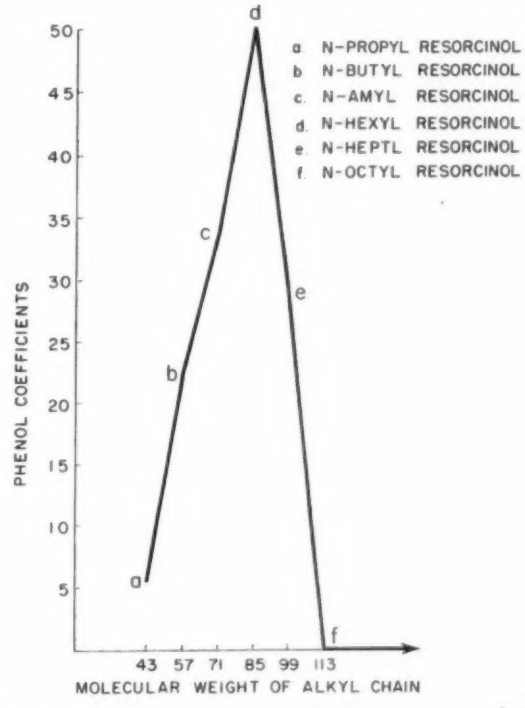

FIG 3 BACTERIAL ACTIVITY OF ALKYLRESORCINOLS (14)

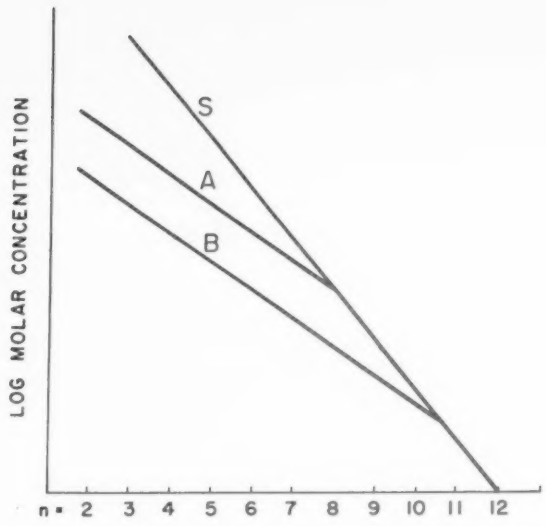

FIG. 4. EQUIACTIVE MOLAR CONCENTRATIONS AND SOLUBILITIES OF HOMOLOGOUS DISINFECTANTS (SCHEMATIC ONLY) (13)

of the phenol coefficient against the increase in molecular weight of the resorcinol derivatives.[14]

Ferguson[9] explained the reason for the sharp "cut off" at a specific point in a homologous series of alcohols as due to a greater decrease in solubility as the series was ascended, in comparison to the decrease in toxicity. For example, the ratio of molar concentration to elicit an equi-toxic effect of primary alcohols was approximately 3 while the molar solubility was a little above 4 between each two successive members in the series. A point then would be reached in which the solubility would not be great enough to permit the necessary concentration of drug to exert its equi-toxic effect. The "cut off" point would be different for each organism; since each organism would have a different degree of resistance to the drugs. This may be shown by referring to Ing's[13] schematic graph (Figure 4) where A and B represent the decrease in equi-toxic effect of two different organisms as a homologous series is ascended. Curve S is the solubility of the disinfectant expressed in the same units and can be seen crossing line A much earlier in the series than line B. This would indicate that for organism A, the toxicity would fall after reaching the point where n is equal to 8; whereas, the toxicity for the more resistant B organism would not fall until n reached a value of 11.

Branched chain alcohols and phenols have usually been found to be less active than their primary chain isomers. This order of activity decreases from normal to secondary to tertiary alcohols. The data for a number of germicidal alcohols and phenols indicate that the compounds primarily act through a physico-chemical action as the "whole" molecule, and that their activity parallels such physical properties as lipid solubility, distribution coefficient between oil-water phases, surface tension, etc.

Molecular Shape

Another physical property of a substance which probably plays a very important part in biological activities is the shape of the drug molecule. This is very evident when a specific substrate influences the activity of the enzyme. The enzyme, be what it may, is a macromolecule having a definite three dimensional arrangement. For the substrate to alter the function of the enzyme, it must enter the macromolecular structure and impinge or fit into the specific site responsible for the enzyme activity. Thus, the three dimensional arrangement of the substrate must fit exactly the shape at the site in the enzyme. Without this very exacting specificity, many other drugs or other foreign bodies would interfere indiscriminately with the enzyme system.

Perhaps the best example of the importance of molecular shape and biological activity may be seen in isomeric substances where one isomer has a very potent biological effect while the other has none. Beckett and Casy[15] succinctly reviewed this aspect of biological activity and sterioisomerism in a past publication.

Another example of molecular shape and biological activity may be seen if *p*-aminobenzoic acid is considered. The biological activity of this compound is diminished if a halogen atom is substituted at the ortho position to the carboxylic group. The activity is progressively diminished as the size of the halogen is increased (*i.e.* from fluorine-chlorine-bromine). Sexton[16] theorizes that the largest halogen atom (bromine) impedes to the greatest extent the approach of the molecules to the site in the enzyme necessary for the biological activity.

Pauling and Pressman[17] have shown that the interaction of antibodies with haptens may be due to the shape of the haptens.

Schueler[18] demonstrated that special arrangement of the molecule of the estrogenic hormones was quite important. For example, he postulated that a substance may have estrogenic activity if there exists a spacial distance between two hydroxyl groups in the molecule approaching 8.55 A. In this respect, Pfeiffer[19] has pointed out that parasympathomimetic activity may be produced if a molecule contains two adjacent oxygen groups, spacially separated by a distance of 5.0 to 7.0 A.

Pitts *et al.*[20] in their investigation of organic compounds of mercury as diuretic agents found that a spacial distance of at least 3 carbon atoms between an atom of mercury and some hydrophilic group seemed to be necessary for diuretic activity.* They postulated "that mercury and the hydrophilic group with this critical spacial configuration bind at two sites to some renal tubular enzyme concerned with reabsorption of salt and water. Inactivation of this enzyme results in diuresis."

*Mercury chloride being disregarded

PHYSICO-CHEMICAL PROPERTIES AND BIOLOGICAL ACTIVITIES OF CYTOTOXIC AGENTS & DRUGS

Part Two

Effect of Ionization

► MANY OF THE MEDICINAL AGENTS in current use are organic substances possessing weakly acidic or basic properties. Their electrical conductivity in water is a measure of their dissociation or ionization. The ionization or dissociation of a weakly acidic drug (HA) may be represented as:

$$HA = H^+ + A^- \qquad (1)$$

To calculate the molar concentration of the anion (A^-) and the undissociated acid (HA), the following formula may be utilized:

$$pH = pKa + \log \frac{(A^-)\ f_{(A^-)}}{(HA)\ f_{(HA)}} \qquad (2)$$

where pKa is the negative logarithm of the thermodynamic dissociation constant for reaction (1), (A^-) the molar concentration of the anion, and (HA) the molar concentration of the acid. The activity coefficient "f" converts the molar concentration to activities and approaches unity in very dilute aqueous solutions.

For practical purposes, the buffer or the Henderson-Hasselbalch equation based upon the law of mass action may be utilized in place of equation (2):

$$pH = pKa + \log \frac{(Salt)}{(Acid)} \qquad (3)$$

This equation implies several approximations; for example, pKa refers to the negative logarithm of an apparent ionization (K) constant which may be obtained from hydrogen ion concentration measurements under a controlled set of conditions such as temperature, ionic strength and concentrations of other solutes. Interionic attractions are not considered, and consequently, molar concentrations are substituted for the activities of the substituents in solution.

It can be seen from equation (3) that the ratio of salt to acid will vary depending upon *p*H of the medium and the pKa value of the acid. For a given acid, therefore, the pKa will be constant and the change in ratio of salt to acid will be influenced solely by the *p*H of the medium. The calculation for the percent ionization of an acid or base is given by Albert.[21] For an acid, equation (4) is used and for a base, equation* (5).

$$\% \text{ Ionized} = \frac{100}{1 + \text{antilog } (pKa - pH)} \qquad (4)$$

$$\% \text{ Ionized} = \frac{100}{1 + \text{antilog } (pH - pKa)} \qquad (5)$$

Figure 5 demonstrates the unlinear relationship between *p*H and ionization of boric acid.[21] A small change in *p*H, especially if the pKa and pH are close, may double the concentration of the ionized molecule and cut into half the concentration of the undissociated molecules. This bears considerably upon the activity of ionizable drugs, since the ionized and undissociated portions of the drug do not usually elicit the same quantitative response in a biological system.

Alkaloidal salts have long been known to penetrate cells with difficulty; whereas, the free base passes through the cell membrane with comparative ease. The early workers in this field attributed the action of a drug as being due either to the undissociated molecule or to the ionized molecule. For example, as the *p*H increases for weakly basic local anesthetics and more undissociated molecules are present, a smaller concentration of drug is required to elicit an equianesthetic effect. Conversely, the smallest concentration

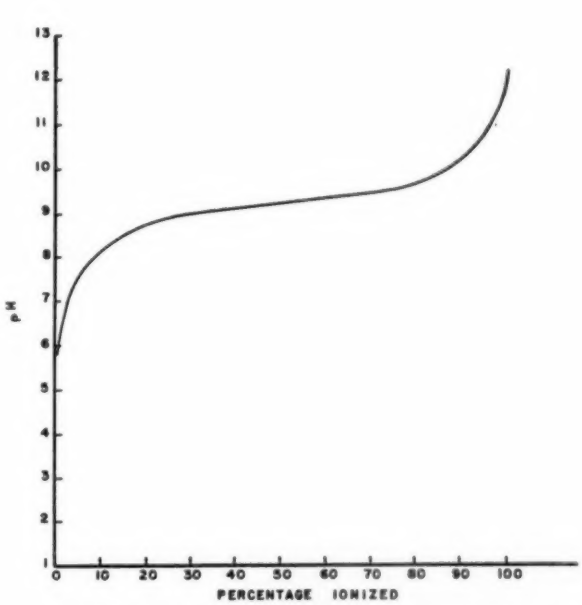

FIGURE 5 TYPICAL CURVE OBTAINED IN THE POTENTIOMETRIC TITRATION OF AN ACID (BORIC ACID, pK = 9.21 AT 20°C). (21)

*Note: pKa may be employed for either acids or bases since pKa=pK*w*- pKb. Often, however, pK*b* values are used to designate the dissociation of basic drugs. In this discussion both pK values will be used.

to exert an equi-anesthetic effect for the acidic barbiturates is at the lower *p*H value. At this hydrogen ion concentration, the barbiturate molecules are essentially in the undissociated form and consequently have little difficulty in passing through the cell membrane. The alcohols, chloroform and chlorobutanol (neutral molecules) are not affected by the changes in *p*H of the medium, their equi-toxic concentration being the same for each *p*H.[22]

For weak electrolytes, the activity of the drug may be due to the undissociated molecule, the ionized molecule or both. At times, it is difficult to attribute the activity to one given molecular or ionic specie. It probably is more correct to visualize that both the ionized and undissociated molecule contribute in varying degrees to the activity. Most drugs must pass from the external environment of the cell through the cell membrane in the undissociated form and then, once inside the cell, to exert their activity either as ions or in the undissociated form. Certain "non-specific" drugs elicit their activity through the neutral or uncharged molecule. The activity of the "specific" type of drug is probably due, for the most part, to the charged molecule which binds to the receptor site in some fashion within the cell causing the pharmacological response. For the sake of simplicity, however, examples of weak electrolytes acting as drugs will be grouped according to the molecular species (undissociated or ionized) which contribute to the greatest *degree to their biological activity.*

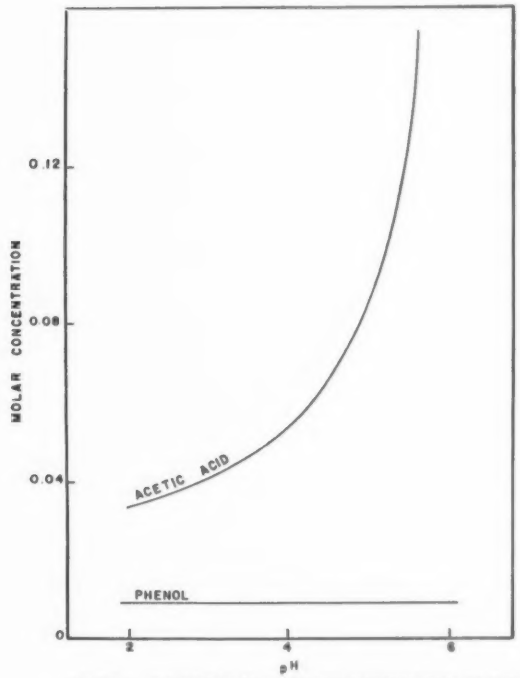

FIGURE 6 THE EFFECT OF pH ON THE CONCENTRATION OF PHENOL AND OF ACETIC ACID REQUIRED TO PREVENT THE GROWTH OF "COMMON MOLD" (26)

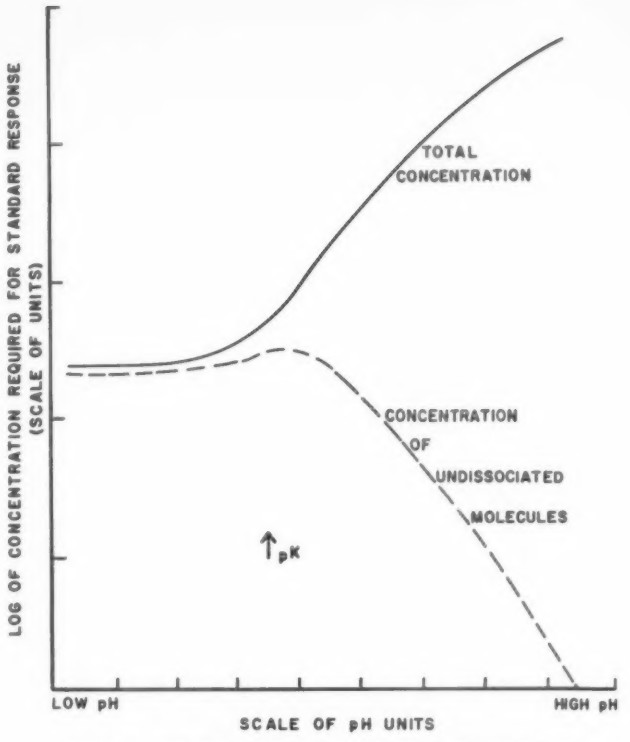

FIGURE 7 THE EFFECT OF pH ON THE CONCENTRATIONS OF A WEAK ACID THAT ARE REQUIRED TO GIVE A STANDARD RESPONSE FROM THE TEST ORGANISM. THE CORRESPONDING GRAPH FOR A WEAK BASE IS OBTAINED BY REVERSING THE pH SCALE. (27)

Activity Due Primarily to Undissociated Molecule

Certain weak organic acids, such as phenols,[23,24] barbiturates[25] and lower carboxylic acids[26] elicit their activity primarily through the undissociated molecule. Figure 6 illustrates the effect of *p*H on the activity of phenol and acetic acid in preventing the growth of "common molds" when equi-effective doses are given.[26] At *p*H 2.5 acetic acid is about ¼ as active as phenol but at *p*H 5.5, it is 1/16 as active. By contrast, phenol is uninfluenced by the *p*H. This is understandable, since phenol has a high pKa (9.9) and, in the *p*H range shown, is practically completely undissociated, whereas acetic acid (pKa, 4.7) will be ionized to various degrees in the same *p*H range.

The biological activity of these compounds is primarily produced by the undissociated molecules, but it should be remembered that at a given *p*H the pKa of the drug will determine the ratio of ionized molecules to undissociated molecules. In this respect, an interesting relation was observed by Simon[27] between the pKa of a drug and the *p*H of the medium for producing a certain biological activity. He plotted the log of concentration required for a standard response in producing a toxic effect on a test organism, against *p*H, as shown in Figure 7. The top unbroken line represents the total concentration of the weak acid while the lower broken line is the concentration of the undissociated molecules. As the *p*H is increased

up to about two *p*H units below the pKa of the weak acid, no change in toxicity occurs. From this point, however, a greater concentration of acid is required to produce equi-bacteriostasis in the test organism. For a weak base, the degree of toxicity is not altered until two *p*H units above the pKb of the drug is reached.

Figure 7 may be employed to predict the change in activity of a certain biological function, such as cell division, respiration, etc., produced by weak acids at various hydrogen ion concentrations.

The activity of tubocurarine* *in vitro* has been shown to decrease as the *p*H of the medium increases. The tubocurarine molecule has four ionizable groups. Two of these groups are quaternary and, consequently, are completely ionized at or near physiological *p*H. Two hydroxyl groups act as acidic groups and will ionize to various degrees depending upon the *p*H of the solution and the pKa. Kalow[28] determined the pKa of both OH groups and found 8.1 for one while the second had a pKa of 9.1. Since the acidities of these hydroxyl groups are different, there may be four different ionizable states at various hydrogen ion concentrations. From the results of a study on isolated frog rectus, Kalow[28] postulated that tubocurarine is more active when its hydroxyl groups are not ionized. As the more acidic OH group (pKa 8.1) ionizes (as the *p*H is increased), the activity decreases. When both OH groups are ionized completely, the molecule becomes inactive.

The undissociated molecule is chiefly responsible in a number of anesthetic agents for the pharmacological effect of the drug. Skou[29] studied five local anesthetic agents (procaine, cocaine, tropacocaine, tetracaine and dibucaine) on their ability to block nerve impulses of the sciatic nerve in decapitated frogs (Figure 8). The blocking ability of these agents decreases as the degree of ionization increases, *i.e.*, at lower *p*H values. Butyl alcohol is included as an example of an non-ionizable agent which has been shown to follow the Ferguson[9] principle.

Activity Due Primarily to Ionized Molecule

In the field of antibacterial dyes, the *p*H of the culture medium has a profound effect on biological activity. The most extensive work on the correlation of ionization of a drug with its pharmacological activity was carried out by Albert on a series of over 100 acridine derivatives.[30,31] This classical work demonstrated that in predicting bacteriological activities, the chemical structure served mostly in influencing ionization. Table V presents these results for a number of acridine derivatives; of the five possible mono-

*Tubocurarine has been included here even though it is in the ionic form. The biological activity, however, is influenced solely by the two acidic (OH) groups.

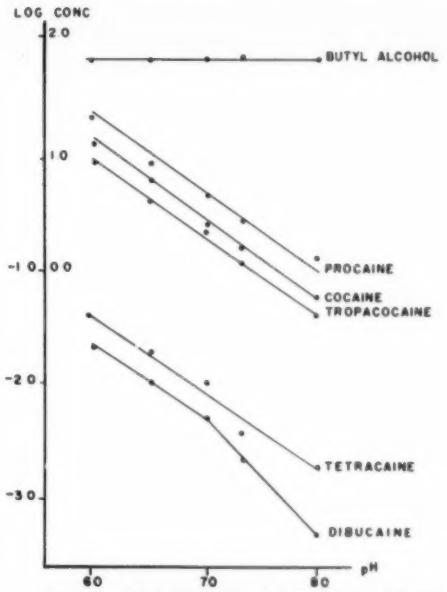

FIGURE 8 THE DEPENDENCE OF THE MINIMUM BLOCKING CONCENTRATIONS ON THE pH . (29)

ABSCISSA pH
ORDINATE THE LOGRITHMS OF THE MINIMUM BLOCKING CONCENTRATIONS IN mM. THE FIGURES TO THE LEFT OF THE ORDINATE APPLY TO TETRACAINE AND NUPERCAINE, THOSE TO THE RIGHT TO THE OTHER NARCOTICS

Table V. Dependence of Bacteriostasis on Ionization in the Acridine Series[30]

Acridine	Min. bacteriostatic conc. for Strept. pyog. after 48 hours incubation at 37°. (Medium: 10 percent serum broth; *p*H = 7.3)	Percent Ionized (*p*H 7.3 = 37° C.)
2-Amino-	1 in 80,000	73
5-Amino-	160,000	100
1:5-Diamino-	80,000	98
2:5-Diamino-	160,000	100
2:7-Diamino-	160,000	76
2:8-Diamino-	160,000	99
5-Amino-1-methyl-	320,000	100
5-Amino-2-methyl-	160,000	100
5-Amino-3-methyl-	160,000	100
5-Amino-4-methyl-	320,000	100
5-Amino-1-chloro-	80,000	83
5-Amino-2-chloro-	160,000	96
5-Amino-3-chloro-	160,000	94
5-Amino-4-chloro-	160,000	86
1-Amino-	5,000	1
3-Amino-	10,000	2
4-Amino-	10,000	2
1:9-Diamino-	5,000	1
3:7-Diamino-	20,000	3
3-Amino-5-methyl-	20,000	3
4-Amino-1-methyl-	20,000	1
1-Amino-9-methyl-	5,000	1
3-Amino-8-chloro-	5,000	1
2-Amino-5-chloro-	5,000	11
2-Amino-7-chloro-	40,000	20
2-Amino-8-chloro-	40,000	33

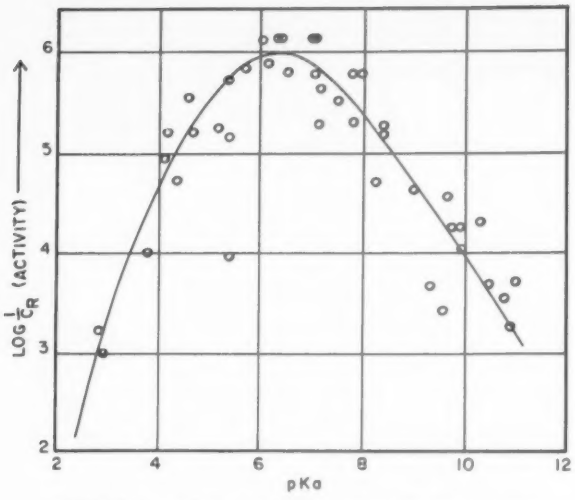

FIGURE 9 RELATION OF IN VITRO ACTIVITY OF SULFONAMIDES TO pKa. (34)

C_R = THE MINIMUM MOLAR CONCENTRATION NECESSARY TO CAUSE BACTERIOSTASIS OF E. COLI IN A BUFFERED (pH 7) SYNTHETIC MEDIUM UNDER STANDARDIZED CONDITIONS

aminoacridines, the two which ionized to the greatest extent at *p*H 7.3 (2-amino- and 5-amino-) are also the two possessing the greatest bacteriostatic activity. Activity increases in this series parallel to the cationic concentration. The introduction of a carboxyl group into 5-amino-acridine at position 3 produces a compound which is dipolar to the extent of 99.8 percent at *p*H 7.3, and this in turn reduces the biological activity to about 1/22 of that of the parent compound. Esterification of the above acid cancels out this decreasing influence. Thus, in this series, the cationic form imparts most of the activity of the molecule; whereas, the neutral undissociated molecule contributes only a small fraction of the bacteriostatic activity. This holds true also for benzacridines, benzquinolines and phenanthridines.

Activity Due to Both Undissociated and Ionized Molecule

Both the undissociated and ionized molecules play a part in the activity of sulfonamides as bacteriostatic agents. Cowles[32] and Brueckner[33] have reported that maximum activity of the sulfonamides occurs when the drug is ionized 50 percent. Unfortunately, this theory could not explain the activity of a number of sulfonamides which do not ionize to an appreciable extent at a *p*H of 7.0.

Bell and Roblin[34] plotted the activity of sulfonamide against their pKa values and found, quite interestingly enough, that maximum activity was reached when the sulfonamides attained a pKa of 6.7 (Fig. 9). They postulated that the magnitude of the negative charge in the $-SO_2-$ group in N′ substituted sulfonamides determines the activity of these drugs as bacteriostatic agents. The greater this negative charge, the more pronounced would be the activity.

The sulfonamides may be shown to resemble *p*-aminobenzoic acid (PABA), an essential nutrient for bacteria, if the structure is depicted as shown in Figure 10. At a *p*H of 7.0, *p*-aminobenzoic acid is in a "non-zwiter ion form" and is 99 percent ionized in solution. The interatomic distance between the two oxygen atoms in PABA and in sulfanilamide is practically identical, while the distance between the hydrogen of the p-amino group and the oxygen atom of either the PABA or the sulfanilamide is relatively the same. The negativity of the $-SO_2-$ group in sulfonamides should approach the negative charge of the $-CO_2$ group in PABA to impart maximum activity. This is a reasonable assumption, since the sulfonamides are antagonistic to and compete with PABA for cell acceptance. The ionic form of the sulfonamides is the active form, for only in this form can it resemble (negative charge) PABA.

It can be seen from Figure 10 that the R group should be responsible for controlling the negativity of the $-SO_2-$ group. In the molecule, both in the undissociated and ionic form, the R group will be competing with the $-SO_2-$ for the negative charge in the amide nitrogen. If the R group is an electron withdrawing group, it will tend to increase the acidic property of the sulfonamide and decrease the electron density residing in the $-SO_2-$ group. This seems to be inconsistent with the relationship shown in Figure 9, but Bell and Roblin[34] clarify this point by making the following remarks:

> It should be recalled here that up to a certain point this decrease in activity with increasing acid strength is more than compensated for by the increasing proportion of highly active ions. Because the ions are much more active than the corresponding molecules, the over-all effect of increasing acid strength produces an increase in activity up to the point where the sulfonamides are largely ionized. Further increases in acid strength are not accompanied by a proportionate increase in the number of ions. The predominant effect beyond this point should be the decreasing negative character of the $-SO_2-$ group accompanied by decreasing activity. Consequently, a maximum would be expected in the curve relating pKa to bacteriostatic activity.

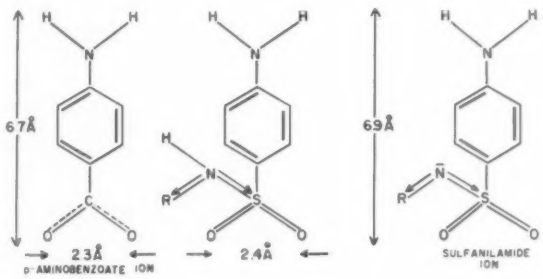

FIGURE 10 GEOMETRIC CONFIGURATIONS OF p-AMINOBENZOIC ACID AND SULFANILAMIDE (34)

Northey[35] applied the thoughts of Cowles and Bruekner[32,33] and developed a mathematical expression which could be used to plot the theoretical activity of the sulfonamides against pKa. The curve produced was in much closer agreement with experimental evidence than the curve of Bell and Roblin (Fig. 9). Northey[35] further postulated that only the neutral molecule penetrated the cell of the bacteria and that the ion was the active molecule at the site of action. A further mathematical refinement was made on the relationship of the sulfonamide activity and pKa by Steinberg, Swindler and Seltzer[36] utilizing the Bronsted Catalysis relationship. It seems that this relationship may be of value in evaluating the biological activity of other weak electrolytes.

For the antihistaminic drugs, activity may be due essentially to their ionized molecules. There appears to be an argument about the role of non-ionized species in this series, probably from conflicting results of various techniques used in pharmacological evaluations and determinations of physical constants. Since the antihistaminics possess basic amino groups, they will dissociate to a certain degree depending upon the *p*H of the solution. All of the clinically useful antihistaminics ionize to a considerable extent at *p*H 7.4. Tolstocuhov[37] attempted to demonstrate the importance of pKb values as an index of *in vitro* activity. By measuring the percentage inhibition of histamine contraction in guinea pig ileum for a number of hydrochlorides of diamines possessing antihistaminic activity, he concluded that the best biological activity was elicited by those antihistamines having a pKb in the range of 5.59 to 6.73, and that other antihistamines having pKb values below or above this range were progressively less active.

Lordi and Christian[38] working with various salts of diamines could not show a definite relationship between antihistaminic activity and degree of ionization. This may be explained partly by the different techniques and methods they used for determining pK constants. Tolstoouhov's data were based upon activity measurements at the highest dilution which imparted a response *in vitro,* because only under these conditions the drop in activity of the most active of the compounds with increase of pKb above a certain level could be demonstrated.

The role of a basic moiety in certain medicinal products such as the analgesics has been emphasized by Beckett.[39-42] One of the features of an analgesic compound is a basic center which will ionize sufficiently at physiological *p*H to associate with anionic site at the receptor surface. However, no relation could be seen between the dissociation constants and the analgesic activity of various agents (Table VI).

Table VI. Dissociation Constants and Activities* of Various Analgesics[40]

Analgesic	pK'a	Approx. analgesic activities (Morphine = 100)
Morphine HCl	8.05	100
Diacetylmorphine	7.83	100
Codeine phosphate	8.22	10
Dihydromorphine HCl	8.15	450
Metopon HCl	8.08	1250
Levorphan tartrate	8.18	200
Nalorphine HCl	7.83	....
Pethidine HCl	8.72	20
-Prodine HCl	8.73	60 - 100
Methadone HCl	8.25	100
Isomethadone HCl	8.07	66
Phenadoxone	6.89	100
6-Piperidino-4:4-diphenyl-heptan-3-one	6.8	100 or 100

*In rats or mice

Brodie[43] reported that the dissociation constants could be utilized for predicting activity of a number of analogs of phenylbutazone whose uricosuric properties increased with the acidity (lower pKa values) of the molecule. Enough evidence is not available to ascertain the contribution of the ionized molecule, but a fair share of the action appears to be due to the ion.

In a study of structure activity relationships of analogs of thyroxine, Kharashch *et al.*[44] found that the pKa of the side chain could be used to some extent to correlate the thyroxine activity of the various analogs.

Drug Absorption in Mammals

Much of the information concerning the physical chemical action of drugs has been accumulated in studies of simple organisms (*Arbacia* eggs, bacteria, erythrocytes, etc.), but relatively little has become known about the importance of *p*H for the passage of medicinal agents through body membranes of higher animals, through certain organs into the blood plasma or from the plasma to the specific organ.

Stomach

Brodie *et al.*[45] have shown that parenterally administered drugs are secreted into the stomach. Since a number of weak electrolytes of dissimilar chemical structure pass through the mucosa of the stomach, the passage of the test drugs was not due to an "active" transport mechanism, but rather to physicochemical properties and was dependent upon pK of the drug. Only those molecules of the weak electrolytes which are lipid soluble (undissociated) will pass through the membrane separating the plasma from the gastric juice. The *p*H of the plasma (7.0) and the gastric juice (1.0) are quite different, and consequently basic drugs will pass through more readily than the more highly ionized acidic drugs.

Contrary to previous thoughts, weak electrolytes which are administered by the oral route are absorbed

from the stomach.[46] In this instance, the stomach is a good organ for the absorption of acidic drugs while a poor organ for the absorption of basic drugs. Once again the mechanism of this phenomenon is based upon the difference in *p*H of the stomach (1.0) and plasma (7.0). The acidic drugs, being the least ionized at a *p*H of 1.0, can pass through the gastric mucosa while the basic drugs cannot. These data are shown in Table VII. It will be noticed, however, that barbital has a very low absorption, and this is explained by its relatively poor solubility in a lipid medium. Acetanilid, caffeine and antipyrine depart from the expected absorption behavior of bases, because they are extremely weak bases and consequently, even at a low *p*H are partially undissociated.

Tetracycline has been reported to be absorbed from the stomach of dogs.[47] Pindell *et al.*[47] indicate that the absorption is passive and most likely is related to the available concentration of the undissociated form of the tetracycline in the stomach.

Intestine

The absorption from the intestinal tract also seems to be dependent upon the *p*H of the intestinal tract and the dissociation constant of the drug. Schanker *et al.*[48] in their studies on intestinal absorption in rats found that the unionized form of the drug was absorbed by simple passive diffusion. The results of their investigation showed that very strong acids and bases were, in effect, not absorbed while those drugs behaving as weak acids or bases were absorbed to various degrees, dependent upon their respective pKa's. For example, those acidic drugs having pKa's greater than 3 and those basic drugs having pKa's less than 8 were absorbed most rapidly.

In one instance, however, Schanker's results[48] appeared not to follow the theory that only the undissociated specie of the drug would be absorbed from the rat intestinal tract. A moderately strong acid, such as salicyclic or benzoic acid, should be in the ionic form at the alkaline *p*H of the intestinal content and thus should not be absorbed rapidly. This was not the case, however, since both of the above-named acids were rapidly absorbed. Further work on these moderately strong acids by Schanker's group clarified the anomalous results.[49] They found that the *p*H of the intestinal content and the absorbing surface of the intestinal wall may be quite different. In this particular instance, they confirmed the thought that in the region of the intestinal wall the *p*H could be slightly acidic.

Table VII.
Absorption of Drugs from Stomach of Rats[46]
(1 hour absorption of 1 mg. of drug in 5 ml. of 0.1 N HCl)

Acids	pKa	percent Absorption	Bases	pKa	percent Absorption
5-Sulfosalicylic	strong	0	Acetanilid	0.3	36
Phenol red	strong	2	Caffeine	0.8	24
5-Nitrosalicylic	2.3	52	Antipyrine	1.4	14
Salicylic	3.0	61	Aniline	4.6	6
Acetylsalicylic	3.5	35	Amidopyrine	5.0	2
Benzoic	4.2	55	p-Toluidine	5.3	0
Thiopentone	7.6	46	Quinine	8.4	0
p-Hydroxypropiophenone	7.8	55	Dextrophan	9.2	0
			Mecamylamine	11.2	0
Barbitone	7.8	4	Darstine	strong	0
Quinalbarbitone	7.9	30	Tetraethylammonium	strong	0
Phenol	9.9	40			

It should be obvious that in a dynamic state such as the body, other factors will alter the extent of the gastrointestinal absorption. The rate and extent of solubility of the drug in the gut, the food content, general health of the animal or patient, administration of other drugs, etc., might be cited as factors altering the absorption rate.

One such factor, solubility of the drug, should perhaps be separately viewed to show its influence upon absorption. For example there are instances where two or more drugs may have the same pKa value yet they will not penetrate a lipoid barrier such as the intestinal wall at the same rate. A suitable explanation for this may be based upon the lipid solubility of the drug, greater solubility producing more rapid penetration.

Brain

Opinions vary concerning the mechanism of penetration of a drug through the blood-brain barrier, but evidence is accumulating that for weak acids or bases the penetration may essentially be passive and dependent upon the *p*H of the medium (blood-brain barrier surface) and the pKa of the drug. Brodie and Hogben,[46] Davison and Luck[50] and Milne *et al.*[51] have presented interesting theses upon this subject with experimental evidence to indicate that it is essentially the undissociated molecule which can penetrate the blood-brain barrier, while the charged moiety (ionized form) has great difficulty in traversing the barrier.

Rall *et al.*,[52] studied the distribution of a number of weak acidic drugs between the blood and cerebrospinal fluid at several *p*H gradients in dogs and concluded that the blood-brain barrier is similar to other biological membranes. They showed that as the *p*H of the blood was lowered the penetration rate of the acidic drugs was increased. This is in agreement with the theory that at lower *p*H values more undissociated molecules will be available to penetrate the barrier.

As mentioned above, the uncharged molecules have considerable ease in passing through the lipoid barrier existing between the blood and the cerebrospinal fluid. A drug, thus, which would have a higher oil solubility than water solubility should have less difficulty in

penetrating the barrier than a drug having greater water solubility. Soloway[53] showed this relationship in his studies on certain aromatic boronic acids upon animals.

Much more investigation must be completed upon this specific subject to elucidate a complete and infallible theory of drug penetration but progress is steadily being made.

Kidney

There have appeared from time to time studies which have related the excretion of drugs from the kidneys to the urine as a function of the *p*H of the medium, pKa of the drug and lipid solubility of the uncharged moiety. Jacobs[54] and Orloff and Berliner[55] may be cited as workers who have contributed information to this field of knowledge.

Summary

Classically the study of pharmaceutical or medicinal chemistry has been based upon the relationship of the chemical structure to the biological activity of the drug or chemical agent. Of recent vintage, however, is the introduction of the principle that certain physicochemical properties might be more useful in studying drug activity. In this discussion, an attempt has been made to indicate how certain physico-chemical properties such as thermodynamic activity, van der Waals' constant, chain length, molecular shape and ionization may affect the biological or pharmacological activity of drugs and general cytotoxic agents.

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Pharmacy-Central Sterile Supply Services

edited by MILTON W. SKOLAUT, *Chief, Pharmacy Department, Clinical Center, Bethesda, Maryland*

► THIS IS A CONTINUATION OF INTERESTING highlights in the packaging and processing of clean and sterile supplies for patients as they affected the eventual development of the Central Sterile Supply Service. Many references to this service now shorten the name to Central Service.

I will continue to use the more descriptive name, since the Pharmacy, X-ray, Pathology, Nursing, Nutrition and many other departments are all central services. Central Sterile Supply Service is incorrect as it pertains to the present operations, since many other patient needs are processed and issued which are not sterile, but simply "surgically clean." Perhaps a name such as "Medical and Surgical Supply Service" would be more correct. Correction of name will be adopted slowly due to tradition.

A 1920 article accurately describes many complaints of operating hospital services of the present day. It discussed the utility room, which doubled for the preparation of trays, instruments and other patient needs. I quote:

> No place has been more neglected in the plans and arrangements of hospitals than has this important factor of the hospital ward unit (utility room). Architects do not appreciate its importance because they have no realization of the work which should be done here. In going through the modern hospitals of the country (1920), one is impressed with the fact that, after the wishes of the medical board and friends of the institution have been incorporated in the plans, any unappropriated space has been utilized for the construction of nurses workrooms without regard to their size or proximity to the wards.[1]

For many years space for Central Sterile Supply sections has been allocated in just this fashion. However, in the last decade the importance of proper location has been recognized by many institutions and appropriate space has been allocated.

Central Supply with Pharmacy

One of the earliest examples of combining Central Sterile Supply with pharmacy was at the California Hospital, Los Angeles, California in 1925. The superintendent of California Hospital reported:

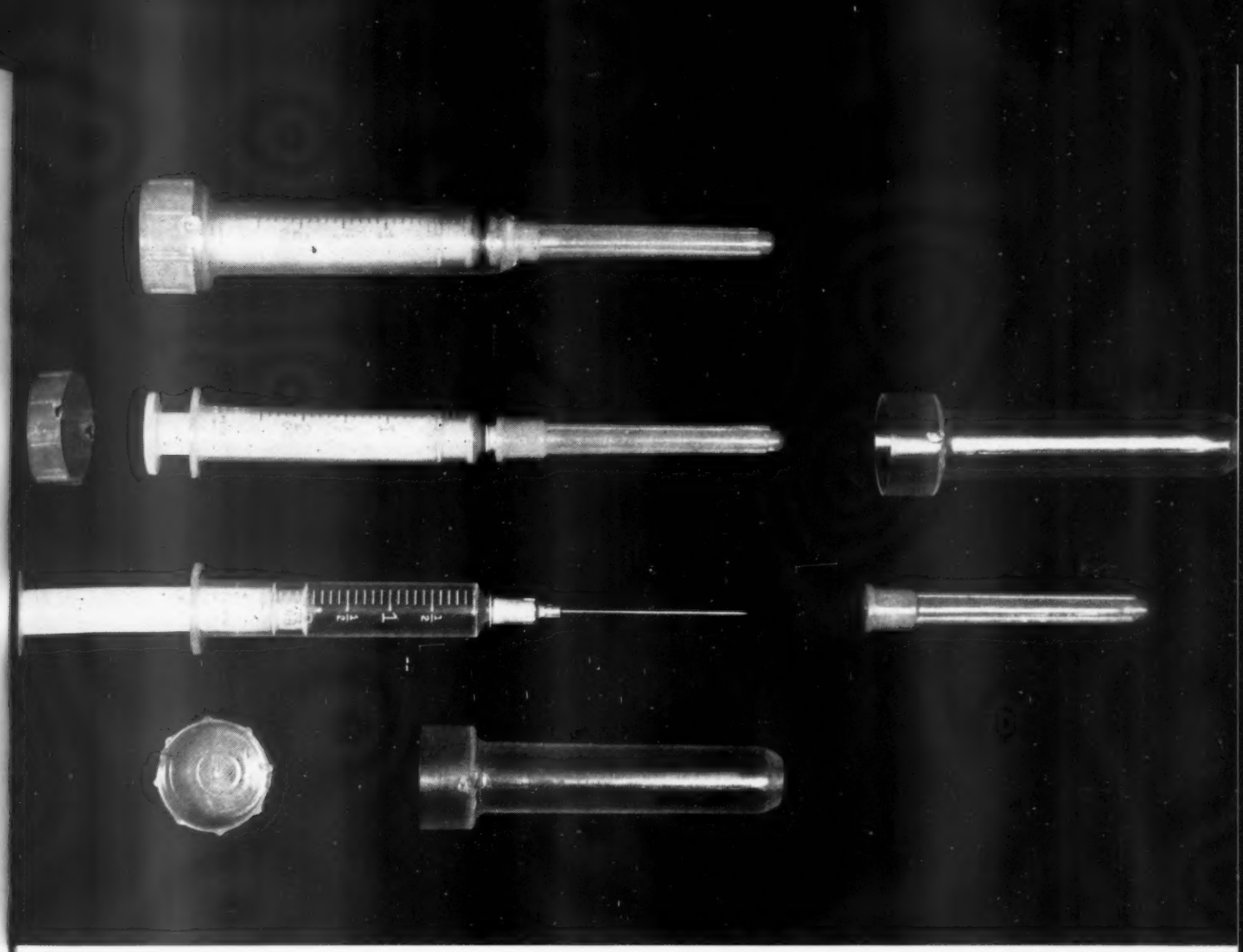
> The pharmacist made a survey of the general treatment trays used throughout the hospital and the particular equipment desired by certain physicians. His survey indicated that many of the items used in treatment tray set-ups were of Pharmacy origin, and that therefore, Central Service and Pharmacy were a logical combination which should prove of value in giving the right type of supervision and consultation with physicians and nurses. As the pharmacist is in charge of both services, he is able to talk intelligently to physicians about their particular tray set-ups, and his knowledge of drugs and chemicals made the added check for assisting the nurses in Central Service. This system also enables all charges to come from the Pharmacy under the supervision of the pharmacist who is acquainted with cost and prices.[2]

Centralization of Service

Miss Alice Gilman, R.N., of Rochester General Hospital mentioned an earlier standardized stocking of sterile supplies and small equipment in hospital. This hospital had equipped each ward with a dressing room, in which articles for treatment were stored. A standard form was devised for restocking and included such items as thumb forceps, dressing forceps, scissors, sutures, and other sterile items. Other items which were added to this form included hot water bottles, ice caps and special thermometers. It is possible to estimate that this system was operating since 1914, but unfortunately the hospital is not identified.[3] This type of standard stocking system is still used. However, it has frequently been increased in scope and more completely centralized.

In 1929 "centralized service rooms" were described and one was established on each nursing unit. These were Central Sterile Supply rooms for each nursing unit and were smaller than the present-day installations, but service was fairly complete. Since these rooms were serviced by nursing personnel from each unit, it reduced standardized procedures of packaging and processing. Following is a partial list of items contained and prepared in these rooms: Instrument sterilizer, hot water sterilizer, sterile and clean vaginal irrigation trays, perineal irrigation trays, sterile catheterization trays, colonic flushing trays, dressing trays, thermometer trays, hypodermic trays, ear irrigating trays, eye irrigating trays, throat irrigation tray, false teeth containers, thermometer glasses, physical examination trays, vaginal examination trays, rectal examination trays, spinal puncture trays, intravenous trays, and stoop trays. In addition, they kept hot water bottles, ice caps, goiter bags, cellu-wipes, rubbing alcohol, lotion, tongue depressors, adhesive, paper cups, bedpans, extension cords, bandages and rubber aprons. All hypodermics were prepared in the room. It contained a crushed ice container, and all narcotics were locked in a drawer.[4]

In 1926, the American Hospital of Paris, France,



Sterile Disposable
Syringe and
Needle

A new sterile syringe with various sizes of needles attached will be available soon. The syringe barrel is made of polypropylene, virtually eliminating incompatibilities. The plunger is linear polyethylene with a non-reactive rubber gasket on its end. The needle is aluminum hubbed with a stainless steel cannula. The unique package provides a syringe sterile outside as well as inside.

opened a new memorial building of 120 beds. Each nursing unit was furnished with complete equipment for all nursing procedures. With seven floors equipped on this plan, it was complete, but complicated, and a considerable waste of material was unavoidable. A Central Sterile Supply was established which distributed supplies to all units, outpatient clinics, and the obstetrical department. A graduate nurse was in charge of the department, and she consulted with the administrative office concerning the buying of equipment and materials.[5] Time after time the waste of materials prior to the establishment of a Central Sterile Supply has been reported. All types and sizes of hospitals have continued to establish these centralized services during the past 30 years.

Hoarding

A 1931 paper entitled "Central Supply Room Overcomes Tendency to Hoard and Hide" was read to the American Hospital Association by Mary Hassett, Assistant Director of Nurses, Merritt Hospital, Oakland, California. Their central supply room had been in operation since 1928. Additional salaries for staffing the centralized services were offset by the savings in dressings, equipment and elimination of waste. Their doctors found the same equipment and supplies in trays throughout the house. It overcame the age-old tendency for the supervisor to hoard or hide supplies.[6] Whether this eliminates hoarding in all institutions is really doubtful. Continuing control from the nursing office is usually required in order to reduce unnecessary hoarding.

The Mary Immaculate Hospital in Jamaica, New York, was operating a Central Supply prior to 1931. In a conference at the American College of Surgeons, Helen Meade reported the advantages and location of a central supply. She stated that the sterilizers were delicate instruments and that only the director of the Central Supply should operate them.[7] Sterilizing equipment has improved considerably to the point of easier and more routine operation, including automatic controls.

Advantage or Disadvantage

Most hospitals have found more advantages than disadvantages in the operation of a Central Sterile Supply Service. Following are some of the advantages of a Central Sterile Supply (Central Service, Medical and Surgical Supply).

> The recognized advantages of centralization are efficiency, economy and safety. When properly organized the system promotes efficiency through good supervision of cleaning, maintenance and sterilization of materials. The problems of standardization, uniformity, and coordination of materials and procedures are more easily controlled because the work is under constant supervision by an individual who devotes her entire time to this activity. A central supply service is also economical because it avoids duplication of equipment infrequently used. The life of materials is prolonged through more efficient handling and better methods of preparation and sterilization. Procedures do not vary from day to day with changing personnel. The use of nonprofessional personnel working under competent supervision, with assembly-line methods and mechanical equipment results in marked savings for hospital. One group of nonprofessional workers whose primary function is the preparation of supplies can be trained to perform exacting technics when the system is highly standardized and adequately supervised. This relieves professional personnel for other duties, not the least of which are patient care activities.
>
> A summary of the advantages of centralization of sterile supplies would be incomplete without recognition of the element of safety. The old decentralized system of sterilization on several floors and in several departments by many people has undoubtedly been responsible for a major percentage of failures in sterilization. Many cases have been recorded where loads of supplies were inadequately sterilized, some where steam was never admitted to the chamber of the sterilizer, and in more than a few instances the entire process of sterilization has been omitted. The evidence against over-sterilization of supplies is equally as bad, if not worse. Here no hazard is involved insofar as unsterile supplies are concerned but the destruction of materials has incurred unnecessary costs for the hospitals. These unsatisfactory practices do not always occur through the fault of the individual but rather because of interference with other, and perhaps, imperative duties. Centralization has taken the operation of sterilizers out of the class of "everybody's business and no one person's individual responsibility," and placed it in a highly specialized class with both supervision and responsibility centered on the shoulders of one responsible person, the central supply service supervisor.[8]

Thermometers and Supplies

In 1927, there was a report of two thermometer baskets for taking patient temperatures, one for oral and one for rectal. The thermometers were sterilized by placing them in a 1:1000 solution of mercury bichloride for one hour. There was one thermometer for each patient at each temperature taking time.[9] Thermometer techniques have progressed through various improvements; including individual thermometers in an individual holder to a centralized service of cleaning and sterilization from the Central Sterile Supply.

A completely stocked plaster cart was designed by the nurses of Gillette Children's Hospital in 1928. It was equipped with every appliance and supply necessary for the application or removal of a cast.[10] Later these carts were stocked and supplied from the operating room or the Central Sterile Supply.

Another early example of a complete tray was a catheter tray in use at The Johns Hopkins Hospital, Baltimore, Maryland, in 1929. It contained all items necessary for routine bladder catheterization. The antiseptic supplied as a part of the tray was Mercurochrome 5 percent Solution.[11] These trays were prepared on each unit, whereas, later these were processed and supplied by the Central Sterile Supply.

Stainless Needle

Most hospital personnel take for granted stainless steel needle cannulas. Probably many have never thought there was ever another type used. In 1925 the "rustless steel" needle became available for general distribution. Prior to that date "it was a problem to have a sharp, bright, sterile needle on hand for immediate use."[12]

While a continuing survey of the historical and interesting background of Central Sterile Supply might be very enlightening, space limitations make this impractical. However, certain historical references will be noted in the context of future presentations.

Next subject: Organization of Central Sterile Supply Service.

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Therapeutic Trends

edited by WILLIAM JOHNSON

Pharmacology Of Petaline Chloride

Petaline chloride is a convulsant alkaloid extracted from *Leontice leontopetalum Linn.* Petaline was found to be a potent convulsant. Tests show the drug to be five to seven times as potent as leptazol. Petaline chloride has muscular relaxant activity and it also depresses the patellar tendon reflex. The drug is more effective than mephenesin in depressing the crossed extension reflex and these effects are similar to those seen when tubocurarine is used. The MLD of this drug is reported to be 3.1 mg./Kg., in mice. It must not be forgotten that the extracts probably contain other substances. Further studies need to be done with a purer compound. The studies were conducted by Ahmad and Lewis and reported in *J. Pharm. Pharmacol. 12*:163 (Mar.) 1960.

RICHARD H. HARRISON

New Treatment Of Trichomoniasis

Trichomoniasis was treated locally by using arsthinol, a new modified compound of 2-3-dimercaptopropanol (BAL), in a one percent solution and in a 50 mg. vaginal suppository in a water-soluble base. The compound has a low toxicity and a clear therapeutic effect in diseases of protozoal etiology. It is lethal to flagella in less than three minutes. The water-soluble suppository base, which liquefies at body temperature, has the added advantage of not producing the discomfort of oil suppositories and the base spreads the drug better, thus permitting its invasion into the folds and creases of the vagina. H. deKanter in *Obstet. Gynecol. 15*:191 (Feb.) 1960 reports the results of tests in 18 patients previously treated by other methods. Good results were obtained in 12, and in 3 others, improvement was obtained but eradication of trichomoniasis was not accomplished. In the last 3 cases only slight improvement was observed. These required a minimum of six weeks of treatment. In a group of 43 patients treated to date, good results were obtained in 38 with a single treatment. It had to be repeated in 5 (3 of whom responded after the second treatment) and in 2 the treatment had to be changed, probably due to infestation by other germs which caused reinfection. In one patient, there was reinfestation after repeated negative slides. However, of the 18 that returned for other reasons, not a single one complained of any trichomoniasis symptoms even after four months. Arsthinol was supplied by Endo Laboratories as Balarsen.

SYLVIA SCHMIDT

Effect Of Disalide On The Intraocular Pressure In Man

The action of a new carbonic anhydrase inhibitor, Disalide, was studied on normal and glaucomatous eyes. Normal eyes, treated with Disalide, showed a decrease in intraocular pressure. Tonograms showed this decrease in pressure to be due to decreased aqueous humor production. Fifty-one glaucomatous eyes were treated. They included 42 simple glaucoma, 6 aphakia glaucoma, and 3 secondary glaucoma. In all but five eyes (10 percent) a decrease in the intraocular pressure was noted. The decrease in pressure ranged from 5 to 66 percent, the average being 34 percent. The effect of Disalide on aqueous hemodynamics demonstrates a 64 percent reduction in aqueous production. The side effects were slight and included some diuresis, and a very definite light headedness. This, however, was only a short term study. Drance and Carr reported the results of their findings in *A.M.A. Arch. Ophthalmol. 63*:540 (Mar.) 1960. The drug, Disalide, 5 chloro-2,4, disulphamyltoluene, was supplied by British Drug Houses Limited.

RICHARD H. HARRISON

Demecarium Bromide In Treatment Of Glaucoma

A new drug, demecarium bromide (BC-48), was used to treat a total of 109 eyes of 59 patients. The drug was supplied by Merck Sharp and Dohme as Humorsol and solutions in percentage concentrations of 0.1, 0.25, and 0.5 were used in the trial. The study conducted by Krishna and Reopall confirmed that the drug is a potent long acting cholinesterase inhibitor. The drug was used as little as twice weekly up to doses of twice daily, in all concentrations. The drug appeared to control various types and various stages of glaucoma. Humorsol controlled intraocular pressure in eyes uncontrolled by conventional glaucoma therapy. BC-48 is readily soluble in aqueous solutions and is stable indefinitely at room temperatures. The test showed that the lower concentrations should be used and that frequency of instillations should be individualized but in no case should the medication be applied more than

twice daily. The drug should be used with caution where the following conditions exist: vasomotor instability, bronchial asthma, spastic gastrointestinal disturbances, hypotension, epilepsy, and Parkinsonism. The study was reported in *Am. J. Ophthalmol. 49*:554 (Mar.) 1960.

RICHARD H. HARRISON

3-Aminophthalhydrazide For Alopecia Areata

The purpose of this preliminary study was to explore the effectiveness of a new potent agent, 3-aminophthalhydrazide, in patients with alopecia areata. Ten patients with alopecia areata were given a 0.05 percent solution of 3-aminophthalhydrazide in sterile water containing 2 percent benzyl alcohol intracutaneously in courses extending over a three month period. Nine patients showed improvement in the growth of hair. There is no doubt that the smaller the affected area, the faster the rate and completeness of recovery. In general, 2-3 weeks after treatment the hairs began to appear as a fine, downy growth from the margin of the affected area, and 2-3 months after treatment, the fine, downy growth was replaced by a crop of thicker and stronger hairs. Shinazo Irie, in *Current Therapeutic Research 2*:107 (Mar.) 1960, explains that the mechanism by which 3-aminophthalhydrazide causes the growth of hairs is unknown and should be studied further. However, it seems that 3-aminophthalhydrazide, which has a β-unsaturated ketone in its formula, may stimulate the growth of hair follicles by reason of its metabolic activity as an oxidation catalyst.

SYLVIA SCHMIDT

A New Antifungal Substance

This study by Allegen and Fisk appeared in *Acta Med. Scandinav. volume 166* (Mar. 10) 1960. This chemical, tetrahydrofluorenone or 1,2,3,4-tetrahydro-9-fluorenone (THF), is insoluble in water, but soluble in various organic solvents. It has a low melting point and is oxidative and light sensitive. It may be sterilized for a short period of time before decomposing. Methods of evaluation included *in vitro* experiments, serological determinations, chemical determination of THF in the serum and in the urine, and clinical studies. *In vitro* experiments demonstrated THF activity on various yeast-like fungi, and it was found to be mainly fungistatic. On chemical analysis of serum and feces, no THF could be demonstrated after oral or intramuscular administration. After oral administration of up to 1.5 grams daily, a maximum concentration of 2.8 mg.% and a maximum elimination of 20 mg./day was discovered in urine samples. The method of determination involves ultraviolet spectrophotometry after cyclohexane extraction. Clinical studies were done on forty patients who had varying types of candidoses of mucous membranes. The drug was shown to be both amoebicidal and antifungal in action.

DALE R. HYDER

A Potential New Therapy For Febrile Seizures

Of sixty new chemicals tested (including phenobarbital), N-phenyl-barbitone was the most potent anticonvulsant as reported in the *Brit. Med. J.* page 1111, (Apr. 9) 1960 by Millichap. The results of initial trials of N-phenyl-barbitone in children with fever and seizures were encouraging and further evaluation of its clinical efficacy against febrile seizures, hyperpyrexia, and minor epilepsies seem warranted according to the author. This chemical and others used in this study were supplied by Burroughs Wellcome and Company Inc., Tuckahoe, N. Y.

KENNETH W. HUCKENDUBLER

New Hypotensive Agent—Bretylium Tosylate

Results obtained from clinical evaluation in patients with arterial hypertension indicate that this new sympathetic blocking agent constitutes an important improvement in the medical treatment of hypertension because of its effectiveness and almost complete absence of parasympathetic blocking action. Addition of a natriuretic drug of the thiazide series, singly or with hydrazine, was found to greatly enhance the hypotensive action of this benzyl quaternary ammonium compound. Side effects showing greatest incidence were dizziness, orthostatic hypotension and digestive complaints. Bretylium tosylate was supplied as Darenthin by Burroughs Wellcome and Company to Genest *et al.* who reported the results of this study in *Canad. Med. Assoc. J. 82*:872 (Apr. 23) 1960.

KENNETH W. HUCKENDUBLER

Tolbutamide In Paralysis Agitans

This report of fifteen cases of paralysis agitans treated with tolbutamide appears in *J. Am. Med. Assoc. 172*:1351 (Mar. 26) 1960 as observed by Gates and Hyman. Tolbutamide was used to relieve some of the characteristic effects of this disease. In twelve of the fifteen cases there was noted either reduction of tremor or rigidity or both. The lessening of rigidity was the predominant result. In several patients there was a marked change in the mask-like facies with return of a nearly normal facial expression. In some patients improvement in speech was noted. It was determined that the improvements were not related to hypoglycemia. Special care was taken to minimize the psychic effect of a new drug. One of the reported cases developed a hypoglycemic reaction but it was felt this was due to the patient refusing to take nourishment as directed. The other patients were fed six times a day which included three meals and three lunches. Most patients were benefited to the extent that they required less care and could perform many more daily living tasks. The significance of these results is not clearly understood and these investigators indicate further research on both animals and man is needed.

DALE R. HYDER

Timely Drugs

Chemipen

GENERIC NAME: Phenethicillin potassium; produced by the N-*a*cylation of a-phenoxypropionic acid (the phenyl ether of lactic acid) and 6-amino-penicillanic acid.

INDICATIONS: Treatment and prevention of penicillin-susceptible infections.

SIDE EFFECTS AND CONTRAINDICATIONS: Occasionally, mild diarrhea or epigastric distress; overgrowth of nonsusceptible organisms.

DOSAGE: 125 or 250 mg. 3 times daily, preferably on an empty stomach; hemolytic streptococcal infections should be treated for a period of not less than 10 days to prevent development of rheumatic fever.

PREPARATIONS: Tablets containing 125 mg. or 250 mg.; syrup containing, when reconstituted, 125 mg. per 5 ml.

PACKAGING: Bottles of 24 tablets; bottles of 60 ml. syrup, when reconstituted.

SUPPLIER: Squibb.

Darcil

GENERIC NAME: Phenethicillin potassium; potassium *a*-phenoxyethyl penicillin.

INDICATIONS: In treatment of bacterial infections due to penicillin-susceptible organisms.

SIDE EFFECTS AND CONTRAINDICATIONS: Allergic reactions to oral penicillin, especially in patients with histories of hay fever, asthma, etc. Loose stools have been reported occasionally.

DOSAGE: 0.25 Gm. 3 times daily.

PREPARATIONS: Tablets containing 0.25 Gm. (400,000 units) phenethicillin potassium.

PACKAGING: Bottles of 36 tablets.

SUPPLIER: Wyeth.

Elipten

GENERIC NAME: Amino-glutethimide.

INDICATIONS: In most types of epilepsy, i.e., grand mal, petit mal, psychomotor, mixed, temporal lobe, and myoclonic seizures.

SIDE EFFECTS AND CONTRAINDICATIONS: Skin rash, beginning within the first week of therapy and rarely continuing more than 5 to 8 days. Extreme caution should be exercised in patients with a definite history of allergy.

DOSAGE: Adults, 0.125 to 0.25 Gm. once a day, increased by same amount every 3 to 5 days. Maintenance, usually 0.75 Gm. 3 times a day. Children under 2 years, 62.5 mg. once daily, increasing gradually to average of 375 mg. daily. Children over 2, 125 mg. once daily increasing by increments of 125 mg. to average of 750 mg. daily.

PREPARATIONS: Tablets containing 0.125 Gm. or 0.25 Gm. amino-glutethimide.

PACKAGING: Bottles of 100 tablets.

SUPPLIER: Ciba.

Humatin

GENERIC NAME: Paromomycin, obtained from culture filtrates of a *Streptomyces*.

INDICATIONS: In patients with certain enteric infections of bacterial etiology or intestinal amebiasis; also in preoperative suppression of normal intestinal microflora and as adjunctive therapy in management of hepatic coma.

SIDE EFFECTS AND CONTRAINDICATIONS: As with other antibiotics, use may result in overgrowth of nonsusceptible organisms, particularly Monilia.

DOSAGE: Bacillary dysenteries, adults, 35 to 50 mg. per Kg. per day in divided doses; children 50 mg. per Kg. per day in divided doses. Amebiasis, adults, 0.75 to 1.5 Gm. daily in divided doses for 5 days; children, 10 mg. per pound daily for 5 days.

PREPARATION: Capsules containing 0.25 Gm. paromomycin (as the sulfate).

PACKAGING: Bottles of 16 capsules.

SUPPLIER: Parke, Davis & Co.

Ostamer

COMPOSITION: A polyurethane plastic.

INDICATIONS: To produce internal fixation of certain long bone fractures requiring open reduction.

DOSAGE: When carefully measured amounts of Ostamer Catalyst and Prepolymer are mixed vigorously, the resulting mixture liberates CO_2 and progresses rapidly from a liquid to a plastic state, resulting finally in a rigid, porous foam. For complete directions on use and preparation, see package literature.

PREPARATIONS: Therapy kit with sufficient material for repair of the typical long bone fracture; includes 61 Gm. of Ostamer Prepolymer, 30 Gm. Ostamer Catalyst, a jar opener, and a wire beater.

SUPPLIER: Wm. S. Merrell Co.

Robaxisal

COMPOSITION: Methocarbamol (Robaxin) and acetylsalicylic acid.

INDICATIONS: For pain associated with or due to skeletal muscle spasm such as that associated with disorders of the back, whiplash and other traumatic injuries, myositis, pain and spasm associated with arthritis.

SIDE EFFECTS AND CONTRAINDICATIONS: Rarely, minor effects from methocarbamol such as dizziness, lightheadedness and mild nausea; contraindicated in patients with idiosyncrasy to acetylsalicylic acid.

DOSAGE: Adults, 2 tablets 4 times daily; children, dosage should be adjusted individually, with 27 to 33.5 mg. methocarbamol content per pound of body weight divided into 4 to 6 doses daily.

PREPARATIONS: Tablets containing methocarbamol 400 mg. and acetylsalicylic acid 325 mg.

PACKAGING: Bottles of 100 and 500 tablets.

SUPPLIER: A. H. Robins, Co., Inc.

THE LAW
of hospital pharmacy

edited by GEORGE F. ARCHAMBAULT

► *Because law is a complex specialty made so because of the existence of a set of Federal laws, 50 sets of state laws, and many county and municipal laws and regulations, the author of the column strongly recommends that when specific legal questions arise, one should always consult an attorney, competent in the local law.*

► MUCH HAS BEEN WRITTEN ABOUT THE FORMULARY system in hospitals in recent months. All the old arguments against the formulary philosophy, in my opinion, have been rebutted well by leaders in hospital administration and hospital pharmacy.

Recently, two new arguments have been advanced in print and therefore need rebuttal in print: (1) That the formulary philosophy is an "administrative policy" *of a hospital* and consists of dispensing a different brand of drug for the drug prescribed, and therefore technically constitutes "actionable substitution" under existing laws in many jurisdictions; and (2) A contract made under duress is void from its inception.

In rebuttal to argument one let it be said that unless a state law clearly states that "blanket authorization" is illegal, (I know of no state with such a "substitution" law and I would hope state and national medical, hospital and hospital pharmacy associations would immediately challenge the legality of such a statute should it ever be placed on the books), then, in my opinion, there is no violation of the "substitution" statute currently in effect. As for the statement that the formulary philosophy is an *administrative hospital policy,* the answer most decisively is, *that it is not,* it is in fact a *medical staff policy,* one drawn up by the Pharmacy Committee of the staff (a committee consisting mainly of medical staff members) and one ratified and approved by the total medical staff.

The second new argument lies in the field of contract law—a sound principle of contract law being improperly used in this instance, in my opinion. The principle being that a contract made under duress is void from its inception, even though it has been honored because of a continuation of the duress or a mistake in judgment. In your course in business law in pharmacy administration at your school of pharmacy, you were no doubt taught that a valid contract results when there is a meeting of the minds plus some other essential elements. You were also taught that if there was "fraud" or a "mutual mistake" concerning the subject matter, or if the identity of the contracting parties was confused or other material terms essential to the contract were misrepresented, or if the agreement was induced by *duress,* no valid contract could result. This is sound law.

"Duress" is defined in Black's Law Dictionary as follows: "Unlawful constraint exercised upon a man whereby he is forced to do some act that he otherwise would not have done." In Bouvier's Law Dictionary "duress" is defined as "personal restraint, or fear of personal injury or imprisonment."

The application of this (duress) principle of law being implied to the formulary philosophy, I assume, runs as follows:—a physician in order to have hospital staff privileges must agree to the rules and regulations of the hospital, one of which is to abide by the formulary system. *Duress* is claimed on the grounds that the signer is forced to sign or be denied hospital privileges. It is a well recognized principle in hospital law that a physician must abide by the rules and regulations of the hospital in order to enjoy the benefits and privileges of being a member of the hospital staff. The rules and regulations must of course be reasonable and not of a caprice or frivolous nature. Obviously, no duress or coercion is used on a physician to force him to become a member of the staff of a particular hospital. He usually *seeks* such an appointment and if the rules and regulations are in the best interest of his patients and

himself, they are rules and regulations he not only willingly signs an agreement to follow, but also insists that a similar statement be signed and obeyed by his fellow staff physicians. Can one honestly state that the rules and regulations surrounding the hospital formulary system as recognized by the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, the American Hospital Association and others are not reasonably sound and in the best interest of the patient and physician? Obviously not.

"Formulary agreements" cannot, therefore, be construed as "duress contracts." What personal restraint can be shown here that is unreasonable in nature? Such agreements are not *void ab initio* in law.

In my opinion, to claim that they are and that "substitution" engaged in under the so-called "protection of the contract" will not receive immunity from the law is more, I suspect, fear psychology than law *per se*.

August H. Groeschel, M.D., Associate Director for Professional Services of The New York Hospital, made a well worth remembering statement in 1957 to the members of the ASHP, "Stand fast in your support of your medical staff, its pharmacy and therapeutic committee, *your hospital formulary*, your policy of rational drug therapy, the use of generic rather than trade names—the validity of your position in support of all these things is attested to by the approval given by the national medical and hospital organizations concerned duly with the maintenance and improvement of the *highest quality of medical care*. Their approval is expressed through their active participation in the inspection and evaluation of hospitals through The Joint Commission on the Accreditation of Hospitals. Take confidence in the fact that you are in good company and that your number is increasing steadily every year."

Tax Free Alcohol and Spirituous Liquor in Hospitals

► WE REPRODUCE in the column to the right the results from the Alcohol and Liquor Questionnaire published in the January 1959 issue of THIS JOURNAL. Although only seven hospitals reported, and the sampling is too meager to draw specific conclusions, there is an indication that outpatient clinics apparently are supported by patient clinic fees and that ethyl alcohol and whisky are still valuable drug agents in every day hospital use. As noted in the chart, reports came from five states—Massachusetts, Michigan, Ohio, New York, and Kansas.

Table 1. Status of Outpatient Departments Using Ethyl Alcohol and Whiskey

Hospital	Beds	Outpatients Annually	Status of O. P. Dept. % Self-Supporting	Fee Charged per O. P. Visit	% Patients Treated Free	% Patients Paying Partial Fee	O. P. Pharmacy Prep. Using Ethyl Alcohol	Whisky Used for	Would You Favor a Patient Receiving the Minimum Amount Packaged in Your Own Liquor State (Pint or Miniature) as a Prescribed Unit?	Comments
1	286	57,000	55	0 to $5	45	–	–	1,6*	No	No	–
2	300	14,088	100	.50 to $2	25	75	–	1,4*	No	No	–
3	110	18,000	100	$5	Under 1	Under 1	–	1,6*	–	–	–
4	337	8,000	0(?)	.25 to $3	97	3	–	1,3,4*	Yes	–	–
5	260	9,000	28	0 to $4.42	29	71	–	1,4,6*	–	–	–
6	132	4,401	25	$3.50 to $7.50	0	10	–	1,2,4*	–	Yes	Pint too large to give to patient.
7	282	22,000	41	$2 to $3	59	31	–	1,2,4,6*	–	Yes	–

*Number Code

1. Senile and aged patients as tonic and appetizer
2. Tuberculosis patients as tonic and appetizer
3. Swab for circumcisions
4. Post-operatively for alcoholics
5. Blood donors
6. Other uses such as cardiac cases, tonic, appetizer, "alcoholic anonymous" wards, hypotensive patients, etc.

★ TEXAS SEMINAR

submitted by LUTHER PARKER *and* HAROLD D. POWELL

► ALMOST ONE HUNDRED Texas hospital pharmacists traveled to Austin, Texas to attend the Twelfth Annual Hospital Pharmacy Seminar on April 8, 9, and 10, 1960. This Seminar was conducted by the Texas Society of Hospital Pharmacists and the University of Texas College of Pharmacy.

The traditional social functions, always well received by the group, were highlighted by an opening "get acquainted hour," a Saturday luncheon and buffet dinner, and a Sunday dinner at the Commodore Perry Hotel. These delightful pauses in the professional activity of the program were offered through the courtesy of E. R. Squibb and Sons, Eli Lilly and Company, Pfizer Laboratories, Lederle Laboratories, Wyeth Laboratories and Cutter Laboratories.

The professional program of the Seminar was designed to offer Texas hospital pharmacists a wide variety of timely topics discussed by nationally known speakers in each field.

Mr. Vernon Trygstad, President of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, Dean James R. D. Eddy, University of Texas Division of Extension, Dean Henry M. Burlage, University of Texas College of Pharmacy, and Mr. Guy Kelly, President of the Texas Society, welcomed registrants on behalf of their respective organizations.

The Executive Council Meeting of the TSHP was held in conjunction with the Seminar. Mr. Max Roesch, Executive Secretary of the Texas Pharmaceutical Association, and Mr. Vernon O. Trygstad, President of the ASHP, were invited to address this group.

Program

Dr. Samuel H. Hopper, Professor of Public Health at Indiana University, opened the technical part of the Seminar with his paper entitled "Hospital Antiseptics and Germicides." Dr. Hooper emphasized that an important consideration in hospital disinfection is "soap and water" cleanliness. The antiseptic will be much more efficient if the area is cleaned before application. The time honored measure of antiseptic activity, "phenol coefficient," was discounted as misleading and unreliable because of many factors that influence the activity of the antiseptic in actual use.

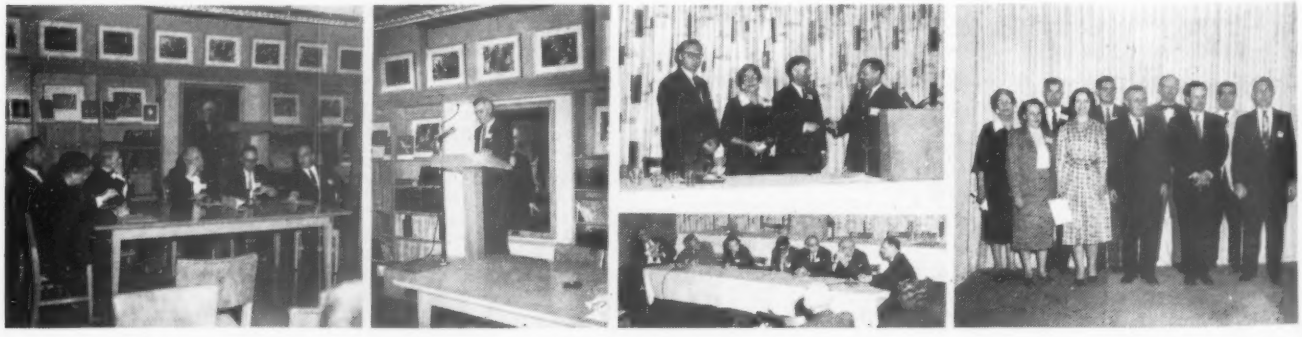
Mr. Paul Wilburn, Chief Pharmacist, St. Luke's Episcopal and Texas Children's Hospital, Houston, described and gave a demonstration of the forms, bottles, closures and procedures used in handling floor stock narcotics in his hospitals. His discussion included the details of the narcotic check sheet, the narcotic inventory record, the narcotic administration sheet, and the packaging of the narcotics for the units.

Mr. Theodore Benya, Assistant Chief Pharmacist, Harris Hospital, Fort Worth, narrated a unique movie on the narcotic procedures, forms, bottles and closures used at Harris Hospital in Fort Worth.

Mr. James McKinley, Chief Pharmacist, M.D. Anderson Hospital and Tumor Institute, Houston, gave a discussion on floor stock control. He presented ways of selecting a floor stock list, both free and charge, and discussed the responsibility for maintenance of these stocks at the nursing level and the importance of regular inspection on the nursing units by a pharmacist.

Dr. William Heller, Director of the *American Hospital Formulary Service,* discussed latest developments of the Service. He listed some new therapeutic classifications which have been suggested to him by pharmacists throughout the nation. A copy of the March 1960 issue of the University of Arkansas Medical Center Pharmacy Bulletin was distributed to illustrate use of a pharmacy bulletin to describe the formulary system to a group of visiting clinical physicians who are not acquainted with the system.

Photos left to right: Panel discussion covering "The Legal Aspects of Hospital Pharmacy in Texas"; Dean Burlage welcomes enrollees; ASHP President Trygstad installs officers of Texas Society; below, educators discuss hospital pharmacy; at the extreme right, ten pharmacists who have participated in five Texas Seminars are photographed



"The NPC's Hospital Relations Program," was discussed by William E. Woods, Assistant to the Executive Vice-President of the National Pharmaceutical Council, New York City. In Mr. Woods' paper, he commented on answers to his original questions posed at the 1959 Annual Convention of the Catholic Hospital Association. These questions, concerning operation of the formulary system in hospitals, were answered by Dr. George Archambault in the February (1960) issue of *Hospitals,* Journal of the American Hospital Association.

In a joint discussion coordinated by the Editor of the AMERICAN JOURNAL OF HOSPITAL PHARMACY, Don E. Francke, and Gloria Francke, ASHP Secretary, editorials and editorial policy as it relates to the SOCIETY were covered. General comments concerning the role of the editor and his responsibility to the SOCIETY were brought out with particular reference to the fact that THE JOURNAL does serve as the spokesman for the organization. Further, it is through THE JOURNAL that members must depend for factual information regarding SOCIETY activities, matters relating to hospital pharmacy practices, and interpretations by leaders in hospital pharmacy.

Discussions, which were open to questions from the floor, covered editorials such as "Outpatient Prescriptions and Hospital Pharmacies," "Joint Committee of the ASHP and A.M.A.," the several editorials concerning "Organizational Needs of the Society," various aspects of the "alleged" substitution problem in hospitals and its relation to the formulary system, and the work of the Pharmacy and Therapeutics Committee.

"The Legal Aspects of Hospital Pharmacy Practice in Texas," a topic of considerable interest to all practicing pharmacists, was discussed in detail by a panel of hospital pharmacists and representatives of the Texas State Board of Pharmacy. It was established that currently the State Board of Pharmacy has no jurisdiction over drugs dispensed to patients in the hospital. This also applies to drugs taken home with the patient when he is discharged, except that those drugs must be properly labeled to comply with the Texas Pharmacy Law. However, the Board does have jurisdiction over prescriptions filled for outpatients in the hospital pharmacy, and this service must be supplied by registered pharmacists.

The Sunday morning session was opened by a panel discussion designed to determine the topic of interest involved when a "Hospital Pharmacist Talks with Pharmaceutical Educators." Dr. Don Francke moderated the panel which was composed of Dr. Vernon Green, Dr. Frank Cosgrove, Dr. W. J. Sheffield, Dr. Jaime Delgado and Dr. E. J. W. Hall, all University of Texas College of Pharmacy faculty members.

The primary consideration of the panel was an evaluation of degree programs—B.S. plus the advanced degree *versus* a six year Doctor of Pharmacy degree. Dr. Francke offered several points in favor of the Doctor of Pharmacy degree. The six year programs in general offered more sound, basic courses, with less emphasis on specialized courses. As a result, the graduate is more capable of acting as a consultant to the physician.

The panel of educators were strongly in favor of the B.S. and advanced degree program, emphasizing that the Doctor of Pharmacy is not an advanced degree and therefore misleading. The basic courses have been strengthened under the five year B.S. program, and more electives are available. Panel members were also of the opinion that the thesis route to the advanced degree is more desirable than internship.

" A Survey of Drug Charges in Hospitals," presented by Dr. Ruth Kroeger, very clearly indicated that many hospitals are still dispensing prescriptions at cost or below. Many hospitals have adopted some pricing system, but there is still a wide variation in prices among hospitals within each state. This situation is certainly undesirable to pharmacy and confusing to the patients. Every chief pharmacist should re-examine his pricing system and consult with the hospital accountant to determine whether his prices should be adjusted either up or down to conform to a sound profitable operation. It seems likely that this would tend to standardize pricing within limits and certainly reduce the frequency of such wide variations.

Group attending 1960 Texas Seminar

Hospital Pharmacists' Exchange Program

► HOSPITAL PHARMACISTS who wish to accept an exchange student during the summer months* under the program worked out between the ASHP and the International Pharmaceutical Students' Federation, are invited to write to Mr. Carl L. Vitalie at the University of Southern California School of Pharmacy, Los Angeles, California. Mr. Vitalie is the Liaison Secretary to the I.P.S.F. in the United States. Mr. Vitalie works cooperatively in arranging for exchange visitors with Miss Anne Savage who is the I.P.S.F. Chairman of Student Exchange located at The Firs, 64 Courtfield Avenue, Harrow, Middlesex, England, and with officials of the ASHP. Requests for exchange visits in the United States have been received from individuals in Ireland, New Zealand, the Philippines, Germany, and Switzerland.

The general plan of the student exchange program is as follows. The student may apply to work or to observe in a hospital pharmacy. The host pharmacist may accept a student for work or observation, whichever plan is mutually acceptable. The exchange period may be from one to six months, usually during the summer vacation period. Students pay their own transportation expenses. All students participating in the exchange program must be covered by health and accident insurance. Insurance may be obtained from the I.P.S.F. or from other sources. The student should receive from the hospital free board and lodging and a small amount of spending money, $10.00 per week, or a stipend sufficient to pay these expenses.

The ASHP has encouraged its member hospital pharmacists to participate in the student-exchange program. Objectives of the program are to allow American students and recent graduates to visit other countries as well to allow foreign students to visit the United States to gain diversified experience in hospital pharmacy and to obtain a knowledge of the cultural and pharmaceutical life of the countries visited. It is not necessary for the hospital to have a formal internship program to participate in the student-exchange program. However, it is important that a rather wide range of professional activities and functions be carried out in the pharmacy department of the participating hospital so that the student-visitor may have an opportunity for diversified experience.

It has been suggested that ASHP Affiliated Chapters may develop a local project whereby a foreign pharmacist may be accepted by an Affiliated Chapter and arrangements made for him to be placed in several hospitals for a period ranging from one to six months. As a part of this program, the Affiliated Chapters could also arrange for an American student to participate in the same type of an exchange program in a European country.

Pharmacist and Pharmacy Student Exchange Program

Sponsored by

International Pharmaceutical Students' Federation

I. OBJECTIVES

A. To offer a stimulus to the profession and participating individuals by promoting the interchange of ideas, knowledge and methods in the practice of pharmacy.

B. To make it possible for foreign pharmacists and students to obtain training in the various areas of hospital and retail pharmacy.

C. To encourage mutual understanding between the people of the United States and the people of other countries.

II. EXCHANGE CATEGORIES

A. Students or young pharmacists who wish to work abroad in retail or hospital pharmacies or in pharmaceutical industry for a period of one to six months. Exchanges are generally ONE month in duration, although intercontinental exchanges may be arranged for longer periods. These students should have completed an internship or practical training period IN DISPENSING of 1 year. (Exchanges are available for pharmacists up to 5 years after graduation).

B. Students who wish to observe the work in a pharmacy and the pharmacy student's way of life. (See III. B., C.)

*Information concerning the exchange program is printed as a matter of information. Contacts may be made for participation in future years.

III. RECEPTION CATEGORIES—for persons anxious to be the host to a pharmacy student from a foreign country. The length of stay of an exchange student is set by the host.

A. Pharmaceutical firms or hospitals which would be willing to allow a foreign student to work with them.

B. Pharmaceutical families where the parent is a pharmacist and a son or daughter is a pharmacy student. If the latter so desires, a direct exchange with the student being received will be made if possible (before or after the visit).

C. Pharmacy students who are in a position to entertain foreign students. Again, if the host student so desires, every effort will be made to effect a direct exchange.

D. Pharmacists without sons and daughters in pharmacy who are willing to allow a pharmacy student to work in their pharmacy.

IV. PROCEDURE FOR THE HOST

A. Select host category.

B. Provide room and board or its equivalent in money plus $10.00 a week pocket money for the exchange pharmacist in category A and D; for category B and C, room and board only. (See V. E.)

C. State the form of accommodation which will be provided, dates and length of stay desired (one to six months) and any preferences as to nationality, age or sex.

V. PROCEDURE FOR THE EXCHANGE PHARMACIST

A. Submit application to the U.S. Liaison Secretary not later than May 15 for summer exchanges, or at least 2 months before the beginning of the exchange.

B. State exchange category desired, education, experience, age, sex, type of pharmacy preferred, countries of preference, period of exchange and knowledge of languages. (Standard printed forms may be obtained from the U. S. Liaison Secretary).

C. Pay a fee of $2.80 (1 pound Sterling) or $5.60 for intercontinental exchanges toward the cost of administration, and a guarantee of $2.80 which will devolve upon the IPSF Student Exchange Committee in case of withdrawal within 2 weeks of the beginning of the exchange. This guarantee will be repaid on receipt of a trainee-report from the student by the Chairman of Student Exchange within three months of the completion of the exchange. Should no exchange be arranged both fees will be returned to the student, except in the case of withdrawal from the exchange by the student if less than one month notice has been given. The total of $5.60 ($8.40 for intercontinental exchanges) should be sent to*: Amsterdamse Bank, Leiden, Holland, c/o Mr. Anton Damen, c.s. IPSF.

D. Present completed form DSP-66 (See VI. C. to the American Consular office to apply for visa (for participants coming to America only).

E. Health and accident insurance is *compulsory* since neither the IPSF nor the host can take any responsibility in this regard. If the exchange pharmacist does not already have such insurance, the IPSF Chairman of Student Exchange will supply him with an application for the International Student Insurance Scheme.

F. The exchange pharmacist must pay for the journey himself and make his own travel arrangements. (Contact the U.S. Liaison Secretary for information concerning special student travel rates.)

VI. PROCEDURE FOR THE RESPONSIBLE OFFICER OF THE SPONSORING ORGANIZATION (ASHP or ACA)

A. Forward names of host pharmacists with dates and preferences to the IPSF Chairman of Student Exchange and the U.S. Liaison Secretary.

B. Concur with selection of a particular exchange pharmacist for a particular pharmacy.

C. Execute and forward directly to the foreign pharmacist the Certificate of Eligibility for Exchange Visitor Status (Form DSP-66).

VII. PROCEDURE FOR THE IPSF

A. Supply applications and information to prospective exchange participants and hosts.

B. Coordinate the procedures of the host, exchange pharmacist and the sponsoring organization.

VIII. COUNTRIES INCLUDED IN THE EXCHANGE PROGRAM

A. Member countries of the IPSF include: Australia, Austria, Ceylon, Denmark, Eire, Finland, France, Germany, Great Britain, Israel, The Netherlands, New Zealand, Norway, South Africa, Spain, Sweden, Switzerland, Turkey, U.S.A., Yugoslavia.

B. Exchanges have been most readily arranged with Germany and Yugoslavia.

C. There have been exchanges with Austria, Denmark, Canada, Finland, France, Germany, Great Britain, Holland, India, Israel, Ireland, Italy, Norway, Sweden, Spain, Switzerland, Turkey, U.S.A., and Yugoslavia.

D. Other countries where exchanges may start soon are Australia, New Zealand, Pakistan, the Philippines, Poland, South Africa, Syria and the Latin America Republics.

E. Countries where no knowledge of the native language is required include Denmark, Finland, France, Holland, India, Ireland, Norway, Sweden, Turkey and Yugoslavia.

IX. RESPONSIBLE OFFICERS OF THE EXCHANGE PROGRAM

AMERICAN SOCIETY OF HOSPITAL PHARMACISTS:

Mrs. Gloria N. Francke
Executive Secretary of ASHP
1020 Ferdon Road
Ann Arbor, Michigan

AMERICAN COLLEGE OF APOTHECARIES:

Mr. Robert E. Abrams
Executive Secretary of ACA
Hamilton Court
39th and Chestnut Streets
Philadelphia 4, Pennsylvania

INTERNATIONAL PHARMACEUTICAL STUDENTS' FEDERATION:

Miss Ann Savage
IPSF Chairman of Student Exchange
64 Courtfield Avenue
Harrow, Middlesex
Great Britain

Mr. Carl L. Vitalie
U.S. Liaison Secretary to IPSF
2630 Severance Street
Los Angeles 7, California

* Payment due after notification of a position.

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1960 ASHP Annual Meeting

THE AMERICAN SOCIETY OF HOSPITAL PHARMACISTS will hold its Seventeenth Annual Meeting in conjunction with the Convention of the American Pharmaceutical Association in Washington during the week of August 14. Announcement of plans for the total Convention and hotel reservations have been sent to all members.

The ASHP will meet during five half-day periods arranged in accordance with the new schedule for the A.Ph.A. Convention. Some minor changes are being made within the sessions in order that a better overall program can be presented. Of particular note is the fact that the House of Delegates will officially meet for two sessions this year. The First Session will be held as usual on Sunday afternoon with the Second Session being scheduled for Thursday morning in conjunction with the Final Business Meeting. It is anticipated that this will offer delegates and members a better opportunity to discuss matters which may have been called to their attention at the Annual Meeting. Further, it is believed that the Address of the President-Elect will be more appropriate at the end of the meeting when he will take office.

The four general sessions will follow the same pattern with the exception that sessions are scheduled over a four-day period as noted below:

Monday, August 15, 1:30 P.M.
ASHP First Session

Tuesday, August 16, 9:30 A.M.
Joint Meeting of the American College of Apothecaries and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS

Wednesday, August 17, 1:30 P.M.
ASHP Third Session

Thursday, August 18, 9:30 A.M.
ASHP Fourth (Final) Session

The H. A. K. Whitney Award Lecture will be held on Monday night and the traditional ASHP Breakfast on Thursday morning.

A meeting of the ASHP Executive Committee is scheduled for Saturday, August 13. Additional meetings will be subject to the call of the President and tentative plans have been made to hold a joint meeting of the 1959-1960 and 1960-1961 Executive Committees on Thursday or Friday, August 18 or 19.

An outstanding program including speakers from the hospital, medical and pharmacy fields has been arranged by the Program Chairman, Mr. Clifton Latiolais. The full program and additional details will appear in the July issue of THE JOURNAL.

Trygstad Honored By North Dakota State

Vernon O. Trygstad, director of the Veterans Administration Pharmacy Service in Washington, D.C., and current president of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, was honored by his alma mater, North Dakota State College, during the commencement ceremonies on May 22.

Mr. Trygstad received one of four Alumni Achievement Awards presented this year, which included a special citation and medal. The awards are reserved for graduates of the college who have achieved outstanding success in their chosen fields of activity. A special committee of faculty and administration considers nominations from former students and faculty each year.

The North Dakota citation recognized Trygstad for his special attainments which include development of residency training in hospital pharmacy, cooperative activity with private hospitals for student instruction, training programs for students prior to licensure and revision of civil service standards for pharmacy positions.

A native of Rice Lake, Wisconsin, Trygstad attended Hamline University of St. Paul before entering North Dakota State. He was graduated from the School of Pharmacy with a B. S. degree in 1936 and spent four years in retail practice in North Dakota and West Virginia. He served two years in the Navy and also worked for the Federal Bureau of Narcotics. He has been employed by the Veterans Administration since 1946 and in 1954 became director.

As president of the ASHP, Mr. Trygstad is well known to SOCIETY members. He was also honored just recently when he received the Michigan Distinguished Service Award and the Andrew Craigie Award. He is a member of many national and international associations, societies and committees.

Hospital Pharmacists Participate in Upper Midwest Hospital Conference

Seventy-six hospital pharmacists registered for the Hospital Pharmacy Section of the Upper Midwest Hospital Conference meeting in Minneapolis, Minnesota on May 13. An outstanding program was coordinated by Mr. William W. Tester, Director of Pharmacy Service at University Hospitals, Iowa City, Iowa. This group, meeting for the second year as a pharmacy section of the Upper Midwest Hospital Conference, met for an afternoon and evening session to hear the following discussions and papers:

AFTERNOON: Presiding, Russell E. Y. Strom, St. Barnabas Hospital, Minneapolis.

"Panel of Practicing Hospital Pharmacists," including the following members and topics:

"Methods of Providing Twenty-four Hour Pharmacy Service," by Louis Balster, Swedish Hospital, Minneapolis.

"Equipment for Use in the Hospital Pharmacy," by Earl Schwerman, Rochester Methodist Hospital, Rochester, Minn.

"Information Sources for Hospital Pharmacy," by Richard Schibonski, Veterans Administration Hospital, St. Cloud, Minn.

"Purchasing and Inventory Control," by Alfred A. Mannino, Hospital Division, Geigy Pharmaceuticals.

EVENING SESSION: Presiding, Neal Schwartau, Rochester Methodist Hospital, Rochester, Minn.

"Welcome," by George P. Hager, College of Pharmacy, University of Minnesota, Minneapolis.

"Laws of Hospital and Nursing Home Pharmacy," by Kenneth Nelson, Jr., Division of Special Health Services, Bureau of State Service, U. S. Public Health Service, Washington, D. C.

"Public Relations as it Applies to Hospital Pharmacy," by C. W. Eckstrom, Eli Lilly and Company, Indianapolis, Ind.

Open Panel Discussion.

► LOUIS GDALMAN, Director of Pharmacy Service at Presbyterian-St. Luke's Hospital in Chicago, spoke as a representative of hospital pharmacy at the Ninth Annual Rutgers Pharmaceutical Conference held in New Brunswick, New Jersey on May 11. Discussions covered mail order prescription dispensing, duplication, and use of generic names for drugs. In discussing product duplication and the use of generic names in hospitals, Mr. Gdalman described the work of the Pharmacy and Therapeutics Committee in the hospital and also pointed out that hospital formularies are not restricted systems but "basically provide the best drugs and prevent duplication."

Other speakers included Robert B. Clark, President, Warner-Chilcott Laboratories; Joseph A. Nicholson, Trenton pharmacist and New Jersey State Board of Pharmacy member; Robert R. Buchanan, Executive Vice-President, Northwestern Drug Co., and President, Federal Wholesale Druggists Association; Thomas M. Rauch, Vice-President, Smith, Kline and French Laboratories, Inc.; and Charles T. Lipscomb, Jr., President, Bureau of Advertising, American Newspaper Publishers Association.

The Conference is sponsored annually by Rutgers University Pharmaceutical Extension Service with Dr. John L. Voigt, Director of the New Jersey State University Pharmaceutical Extension Unit, serving as Conference Secretary.

Eugene Von Stanley, immediate past president, New Jersey Society of Hospital Pharmacists, Mrs. Florence S. Frick, president, and Louis Gdalman, director of pharmacy services, Presbyterian-St. Luke's Hospital, Chicago, discuss mutual problems between sessions of the Ninth Annual Rutgers Pharmaceutical Conference held at the New Jersey State University, Newark, on May 11

Foster Named Whitney Award Recipient

Thomas A. Foster

Mr. Thomas A. Foster, Pharmacist Director, Public Health Service, Department of Health, Education, and Welfare, has been named the 1960 recipient of the Harvey A. K. Whitney Lecture Award for his outstanding contributions to American Hospital Pharmacy.

The Whitney Lecture Award was established in 1950 by the Michigan Society of Hospital Pharmacists to honor the first Chairman of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, Mr. Harvey A. K. Whitney, who was active for many years in hospital pharmacy organizations and was largely responsible for the creation of the ASHP.

Mr. Foster is a career pharmacist in the Regular Corps of the U. S. Public Health Service. He began his government career as a hospital pharmacist through a qualifying examination and entered on duty with the Public Health Service in Mobile, Alabama in 1933. This part of his career was preceded by the practice of his profession in retail stores in Birmingham as a lifetime licentiate in the State of Alabama. Following the assignment in Mobile, he served several years as Administrative Officer in the PHS Hospital at Baltimore and its Outpatient Clinic in Washington.

In July of 1942 Mr. Foster began an eight-year assignment as Chief of Supply and Procurement of the Public Health Service. This period covered the difficult war years and the rapid expansion of the responsibilities of the Service.

At the beginning of the Korean War, when the Department of Health, Education, and Welfare received major delegations covering claimancy responsibilities in the hospital and school construction areas, Mr. Foster was assigned to a newly created division in the Office of the Surgeon General organized to discharge these responsibilities. His operations were in the medical and hospital supply area, and principally involved the presentation to mobilization authorities of

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the amount of basic essential items required for the civilian hospitals and other facilities providing medical care for the total population.

This emergency planning work for medical supplies was continued after the Korean armistice, and data were developed on the needs of the civilian population for essential medical items, together with production capability of industry. This work was supported actively by all elements of industry engaged in production of medical supplies and equipment.

At the request of the Office of Defense Mobilization, Mr. Foster was detailed to that organization on January 1, 1958. He is now serving as Health Supply Liaison Officer within the Office of Civil and Defense Mobilization (created by merger of the Office of Defense Mobilization and the Federal Civil Defense Administration in July 1959) and other responsible government agencies. He is also Chairman of Interdepartmental Committees engaged in developing supply-requirement analyses of survival items in the medical supply and water and sanitation supply areas. These analyses will contribute towards future policy of the federal government on stockpiling of medical items.

Mr. Foster is a member of the American Pharmaceutical Association and has been active not only in the parent organization but with the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS as well. He has made contributions to the literature as well as having presented papers at pharmaceutical meetings and seminars. Mr. Foster serves on the A.Ph.A. Standing Committee on National Defense and Security and also the International Relations Committee. He is a life member of the Association of Military Surgeons. He has served that group as a member of the Executive Council for the past six years, and in 1955, was the recipient of its Founders Medal bestowed for distinguished service to the Association.

Mr. Foster is also a member of the International Pharmaceutical Federation and a member of the Royal Society of Health of England, and received official recognition from the Swedish Minister of Health for his assistance to medical personnel of that country.

He is a member of the Army and Navy Club and the Vincent Costello Post No. 15 of the American Legion.

Mr. Foster is married and lives in Washington, D. C. at 3900 Cathedral Avenue, N. W. He has two married children—a son now in the Middle East and a daughter living in Maryland—and two grandchildren.

The Whitney Award presentation will be made in conjunction with the Lecture to be presented by Mr. Foster at a testimonial dinner scheduled for August 15. This dinner honoring Mr. Foster is being held in conjunction with the Annual Meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS and the Convention of the American Pharmaceutical Association in Washington, D. C.

► PAST PRESIDENTS Robert C. Bogash and George F. Archambault attended the "Salute Dinner to Dr. Robert L. Swain," held at Hotel Commodore in New York City on May 12. President Vernon O. Trygstad, who had planned to represent the SOCIETY, was unable to attend. The dinner honored Dr. Robert L. Swain, Editor in Chief, *Drug Topics, Drug Trade News* and *Drug Topics Red Book,* for his contributions to pharmacy for over a half century.

► HOSPITAL ADMINISTRATORS throughout the nation have recently received a copy of the "Suggested Regulations for Handling Narcotics in Hospitals," which has been made available by the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. In transmitting the document to administrators, Secretary Gloria Francke pointed out that this is the result of several years of study by a special committee of the ASHP and the regulations have been approved in principle and recommended for use in hospitals by the Executive Committee of the ASHP and the Board of Trustees of the American Hospital Association. It is further stated that "in developing *'suggested rules'* and 'control systems' for handling narcotics in hospitals, it was our intention to clarify the existing regulations so that pharmacists and other personnel concerned with handling narcotics in hospitals might be better informed regarding procedures which comply with the regulations of the Bureau of Narcotics."

Additional copies of the reprint are available for twenty-five cents each (fifteen cents for 10 or more copies) from the Division of Hospital Pharmacy, American Pharmaceutical Association, 2215 Constitution Avenue N. W., Washington 7, D. C.

► JOSEPH F. TOOMEY, Chief, Pharmacy Services, Rapid City Central Pharmacy, U.S. Public Health Service Indian Hospital, Rapid City, South Dakota, has recently been elected to the position of Secretary of the Rapid City Pharmaceutical Association.

► E. W. NOLLAU, Assistant Chief Pharmacist, University of Chicago Clinics, has recently been named Chief Pharmacist at The Hospital for the Women of Maryland in Baltimore. Mr. Nollau, prior to accepting the position at University of Chicago, was Director of Pharmacy Service for the United Mine Workers.

PHS Pharmacists Participate in Clinical Society Meetings

Hospital pharmacists in the United States Public Health Service participated, for the first time, in a pharmacy section of the U. S. Public Health Service Clinical Society meeting in Staten Island Hospital, Staten Island, New York on May 5. In recognition for the best paper presented at the section, Mr. Philip R. Hugill, Clinical Center, National Institutes of Health, received first prize. The paper, "Ophthalmic Preparation Apparatus," which was authored by Philip R. Hugill, Boris J. Osheroff and Milton W. Skolaut, will be published in a forthcoming issue of the AMERICAN JOURNAL OF HOSPITAL PHARMACY.

Other papers presented at this section were as follows:

"Techniques and Control in the Preparation of Pharmaceuticals as Employed at the U.S. Public Health Service Medical Supply Depot," by Salvatore D. Gasdia, PHS Medical Supply Depot, Perry Point.

"Human Motive in Communication," by Joseph P. Crisalli, Norfolk.

"A Spectrophotometric Procedure for Determining Total Protein in Allergenic Extracts," by E. C. Brennan, New Orleans.

"A Kinescope Presentation of the Pharmacy Department, The Clinical Center," by Milton W. Skolaut, NIH Clinical Center, Bethesda.

"The Pharmacist as a Member of the Hospital Team with Particular Reference to the Artificial Kidney," by Arthur W. Dodds, Lowell R. Pfau, and Dudley Miller, Staten Island.

"Packaging Pharmaceuticals in Polyvinyl Alcohol Film," by Philip R. Hugill and Milton W. Skolaut, NIH Clinical Center, Bethesda.

"Sterile Hemiacidrin Solutions," by Robert P. Chandler, M. Thomas Wegner, Jr., and Arthur W. Dodds, Staten Island.

"Pharmacy Reports: How Can They be Improved?" by George F. Archambault, Pharmacy Liaison Officer to the Office of the Surgeon General.

"Responsibilities of the Pharmacist and Hospital Administrator Concerning Radioactive and Investigational Drugs," by Milton W. Skolaut and Robert M. Farrier, NIH Clinical Center, Bethesda.

"Consideration of Some Aspects of Drug Storage with Particular Reference to 'Keep in a Cool Dry Place'," by Arthur W. Dodds, Staten Island.

► ASHP PRESIDENT VERNON O. TRYGSTAD presented a talk on "Our Professional Responsibilities," at a seminar on June 9 at Howard University, Washington, D. C. He also addressed the senior class at Howard University on June 10.

Pharmacy Section Session, U.S. Public Health Service Clinical Society's Fourteenth Annual Meeting, PHS Hospital, Staten Island, N. Y.

as the president sees it—

VERNON O. TRYGSTAD, *Veterans Administration, Washington, D. C.*

► DO YOU REMEMBER THESE?

A.Ph.A. Resolution (1955)

> *Whereas,* it is agreed by all pharmaceutical authorities that generic names mean the common, chemical, or unregistered names of drugs, or the names recognized by the U. S. Pharmacopeia, the National Formulary, or the Homeopathic Pharmacopoeia of the United States, or the names adopted by the Council on Pharmacy and Chemistry of the American Medical Association, and *Whereas,* the use of generic names is, therefore, in keeping with the highest ethical standards of the medical and pharmaceutical professions,
>
> Be It Resolved, that the American Pharmaceutical Association, as such, believes in and encourages the use of generic names for general drug products.

The Council directed the Secretary to publicize this resolution. (*J. Am. Pharm. Assoc. Pract. Pharm. Ed. 16*:365 (June) 1955.)

A.Ph.A. Resolution (1956)

> Resolved, that the American Pharmaceutical Association support and encourage the use of generic names in the prescribing and dispensing of drugs by the medical and pharmaceutical professions.

The House of Delegates approved this resolution as a reiteration of the official stand of the Association on this subject. The Council directed the secretary to publicize the resolution (*J. Am. Pharm. Assoc. Pract. Pharm. Ed. 17*:302 (May) 1956.)

The foregoing resolutions, adopted in 1955 and 1956, represent the official position of our parent organization, the American Pharmaceutical Association, and to my knowledge, have not been altered or rescinded by any official action of the Association.

RECENT CONFUSION

Recent events have produced a bumper crop of new experts on the advantages and disadvantages of generic names for drugs. Much discussion has resulted from the Senate Subcommittee hearings. Other interests have been stimulated by proposed legislation and state board of pharmacy rulings. Popular magazine articles have also touched on the subject and stimulated interested and varied comment. The outstanding product of all this, to the general public, seems to be utter confusion.

There are those who believe that the prescribing and dispensing of drugs by generic name automatically will result in a significantly lower price. There also are those who would have you believe that the prescribing or dispensing of a drug by its generic name will most likely result in the patient's receiving an inferior product. Either may be true under some circumstances. Neither possibility is necessarily so. There is no reason why the calling of a drug by its correct, official name should necessarily result in either a lower price or an inferior product. It may depend to a great extent on the application of other principles which we should not let get out of focus.

You will note that nearly every argument against generic name dispensing is based on the premise that it will result in the use of poorer quality drugs. This would imply then, that if the pharmacist is given the responsibility for selecting the brand or the supplier of the drug to be dispensed, that he most likely will use a cheap, inferior product, disregarding patient welfare and safety—and with concern only for price, profit, or the saving of a few cents on a purchase. But it is, of course, entirely possible to use generic names in prescribing and dispensing drugs and still have those drugs selected from among the products of reliable manufacturers. And the product can be up to standard if the pharmacist uses his best professional judgement in selecting it, and the manufacturer from whom he buys it.

PROFESSIONAL STANDING CHALLENGED

It is not my purpose to "sell" the use of generic names. There are many sound reasons for their use well known to most of us, but there are others who feel strongly about the advantages of the exclusive use of trade names. Certainly this is not all one-sided. But in our consideration of this question, let us look at its relationship to the professional standing of the pharmacist—especially the hospital pharmacist, and how the public and his professional colleagues view him.

It seems to me that in this matter, the professional stature of pharmacy is at stake. Many manufacturers pride themselves on and advertise their scientific and professional integrity. The professional standards of the physician are generally accepted and no one questions that, in prescribing drugs, he has only the welfare of his patient in mind. But where does the pharmacist fit into this picture? Is it true that in the manufacturer-physician-pharmacist-patient relationship, it is only the

pharmacist whose professional judgment and integrity cannot be relied upon, along with the questionable manufacturer or repackager operating on the fringes of professional respectability? If it is, and it is necessary for a physician to resort to the use of a trade name rather than the official designation of a drug in order to be sure that the pharmacist will not dispense a product of questionable quality—then we have a serious situation that needs correcting. But I am *not* willing to concede that the profession of pharmacy, as represented by the majority of pharmacists, is in any sense inferior to the manufacturer or the physician in the realm of professional ethics and interest in patient welfare.

PACKAGE PURVEYOR

It may be that some of the "broad brush" treatment pharmacy receives stems from the attitude of some in regarding a prescription or a prescription drug as just another item of merchandise—an item of merchandise to be bought at as low a price as possible, and the margin of profit attesting to the astuteness and business acumen of the pharmacist. This may well be one reason why the opponents of generic name usage would relegate the pharmacist to the role of a purveyor of packaged merchandise, ordered by specific trade name, with the pharmacist perhaps enjoying the privilege of opening the container and relabeling it. But there is just one thing wrong with this picture. I do not believe that the profession of pharmacy and particularly hospital pharmacy, is willing to accept this role without challenge.

Much has been said in recent years about the role of the pharmacist as an expert on drugs—as a consultant to the physician on the selection and use of drugs. We believe that in many cases the pharmacist is qualified and can discuss intelligently the pharmacology, therapeutic uses, and comparative properties of drugs. But even if we assume that the physician is equally well qualified to evaluate these factors, certainly the training and background of the pharmacist should make him the undisputed, best qualified individual to judge the pharmaceutical properties of drugs. Who should be better qualified than the pharmacist to evaluate and discuss tablet coating, solubility and friability, flavoring and masking agents, vehicles and bases, and the many other elements of pharmaceutical compounding? And aren't most of the differences allegedly setting one brand apart from another essentially pharmaceutical differences? You will recall the NPC (National Pharmaceutical Council) pamphlet put out a few years ago in an effort to urge physicians to use brand names. Nearly every one of the "24 reasons" for use of brand names had to do with the pharmaceutical aspects of drug products. But I have not seen the recognition, or the suggestion, that the pharmacist might be the most logical one on the health care team to evaluate these differences.

PHARMACISTS ARE RESPONSIBLE AND RELIABLE

During the hearings of the Anti-trust and Monopoly Subcommittee, testimony was given as to the adequacy of *U.S.P.* and *N.F.* standards. Unquestionably, if adhered to, they are sound and reliable. But some doubt was raised as to the unqualified reliability of all drug products purported to be of *U.S.P.* standard quality because of the absence of universal quality control and testing. A question was raised that, if all manufacturers cannot be relied upon to maintain *U.S.P.* standards, how can the physician and the patient be assured of a quality product when it is prescribed by generic name? Unfortunately, this question went unanswered. It is unfortunate because I believe there was a good and logical answer. I believe that the physician *can* have complete confidence in the product dispensed, regardless of the nomenclature used, if he can rely on the pharmacist dispensing it.

And how can the pharmacist know the quality of the product he dispenses? That it does measure up to official standards? It is his business to know. Some pharmacists, especially in hospitals, can carry out tests and assays or have them done. If this is not possible, it may be best to rely upon the reputation and known standards of the manufacturer, and surely this any practicing hospital pharmacist knows or can find out. We might borrow and paraphrase a slogan from the jewelry trade, "If you don't know the quality of the drug, know the manufacturer."

As I see it we need to get our thinking straight on some of our basic principles. First of all, let's be professional, and if we are delegated the responsibility for selecting the manufacturer of drugs we dispense, let's apply our knowledge of pharmacy, and of our manufacturers and suppliers, to assure that our drugs are of the quality expected by the prescriber. Then let's correct the impression that generic is synonymous with "cheap" or substandard. The *U.S.P.*, long recognized as our highest and most respected professional and legal standard; the *National Formulary*, published by the American Pharmaceutical Association, and considered one of its "prestige" endeavors—both use generic nomenclature. The standards of these, even though questioned by some, are still as sound and reliable as they have been in the many years past.

We can and should rebuild the stature of pharmacists as the most knowledgeable link between the producer and consumer of pharmaceuticals; restate our confidence in the standards of the *U.S.P.*, *N.F.*, and other recognized compendia; and leave no doubt that in the selection and dispensing of drugs, the practicing pharmacist is as interested as any on the health services team in the welfare of the patient and in assuring that he receives a quality product.

SELECTED PHARMACEUTICAL ABSTRACTS

and summaries of other articles interesting to hospital pharmacists

edited by CLIFTON J. LATIOLAIS, HENRY J. DEREWICZ *and* LEO F. GODLEY

BACTERIOLOGICAL MEDIA

The Examination of Proteose-Peptone—A Study of Bacteriological Media, Habeeb, A., J. Pharm. Pharmacol. 12:119 (Feb.) 1960. (Sterling Chemistry Laboratory, Yale University, New Haven, Conn.)

Proteose-peptone is recommended as an ingredient of bacteriological media for the production of toxins. The purpose of this study is to examine it to see whether it has any characteristic features to distinguish it from the bacteriological media previously examined. Free and total amino acids content of 3 batches of proteose-peptone are presented. The presence of hydroxy-proline and the high content of glycine and analine suggest that part of the protein used in manufacture belongs to collogen. The three batches have shown streptogenin activity.

THOMAS E. ARKINSON

BETA-PROPIOLACTONE STERILIZATION

Hospital Decontamination with Beta-Propiolactone Vapor, Woodward, M. F. and Clark, A. B., U.S. Armed Forces Med. J. 11:459 (Apr.) 1960. (U.S. Army Medical Unit, Fort Detrick, Md.)

The procedure for decontamination with beta-propiolactone vapor was developed by the U.S. Army Chemical Corps, and has been used three times within the past year for hospital disinfection. These tests have shown that beta-propiolactone vapor used under appropriate conditions is an effective sporicide and bactericide. The rate of action was found to be directly related to the concentration, humidity, and temperature at which it is used. In addition, the vapors did not have a deleterious effect on most metals, plastics, and textiles in concentrations and time exposures effective for disinfection. At indoor temperatures the vapor does not create a flammable mixture in air, but is irritating to the mucous membranes. Laboratory studies indicate that beta-propiolactone used as a vapor-phase disinfectant is approximately 25 times more active than formaldehyde, 4000 times more active than ethylene oxide, and 50,000 times more active than methyl bromide against the spores of *Bacillus subtilis* var. *niger*. However, beta-propiolactone does not possess the high degree of penetration or the effectiveness of ethylene oxide at low relative humidities. The time required to aerate a room or building is much less than that needed for formaldehyde; one or two days with open windows or doors and only a few hours with forced ventilation.

The procedure for disinfection of a single room or of the main hospital building is given in detail with mention of the cubic feet disinfected, time required, and approximate costs.

DAVID BURKHOLDER

LYSOLECITHIN SOLS

A Light-Scattering Study of Lysolecithin Sols, Robinson, N. and Saunders, L., J. Pharm. Pharmacol. 11(Suppl.):115T (Dec.) 1959. (Department of Physical Chemistry, School of Pharmacy, University of London, Brunswick Square, W. C. 1)

Aqueous sols of 4 different samples of lysolecithin (A, B, C, and D) were prepared by the action of viper venom on hen egg lecithin. The 4 samples were studied by means of a light-scattering apparatus. The results of a large number of measurements were analyzed statistically. They indicate for samples A, C, and D that the mean molecular weight of the micelles in the sols is 92,400, the experimental error in this estimate being 7%. For sample C, the limits of molecular weight estimate were more than twice as wide as those for samples A, B, and D. Sample C was recrystallized from a batch prepared some months earlier and may have contained some fatty acids. The results for sample C illustrate the uncertainty of physical measurements on materials derived from biological sources; in such work it is desirable that many results should be obtained with different samples of the substance. The results can then be summarized by making a statistical analysis.

JAMES W. STOVER

ANTIBACTERIAL EFFECT OF MERCURY COMPOUNDS

The Antagonism of the Antibacterial Action of Mercury Compounds Part III. The Effects of Certain Sulphydryl Compounds on E. coli I, Cook, A. M. and Steel, K. J., J. Pharm. and Pharmacol. 11(Suppl.):157T (Dec.) 1959 (Department of Pharmaceutics, School of Pharmacy, University of London, Brunswick Square, London, W. C. 1.)

The antibacterial activity of cysteine, glutathione, thiogycollate, dimercaprol and horse serum to *E. coli* I has been studied. Incorporation of the antagonists into the medium had little effect upon it. With the antagonists incorporated into the dilution blanks the results were as follows. In all dilutions of serum the mean count was significantly greater than that obtained using water as a diluent, but there was no significant difference between the counts with the different dilutions. Cysteine and glutathione in concentrations up to 0.25% appear to have little effect upon the viability of *E. coli* I. The use of a 0.25% thioglycolate solution as the diluent resulted in a significant reduction in viability. Dimercaprol in concentrations above 0.1% causes a marked reduction in the viable count of the organism. From these experiments the following concentrations of the proposed antagonists appear to be suitable for quantitative work involving viable counts of *E. coli* I:

Normal horse serum	up to 20 %
Cysteine	up to 0.25% (about 15 mM)
Glutathione	up to 0.25% (about 8 mM)
Thioglycollate	up to 0.1 % (about 10 mM)
Dimercaprol	up to 0.05% (about 5 mM)

JAMES W. STOVER

GELATIN AND SODIUM ALGINATE

Interfacial Tension Between Gelatin and Sodium Alginate Solutions and Benzene, Shotton, E. and Kalyan, K., J. Pharm. Pharmacol. 12:109 (Feb.) 1960 (School of Pharmacy, Univ. London)

Part I of the article describes studies conducted on the effect of time and concentration on interfacial tension. Both substances displayed a lowering of interfacial tension with benzene and both tension-concentration curves were similar in shape. The authors suggest that a condensed multilayer, which has the physical properties required to stabilize emulsions, is built up immediately below the surface.

Part II of the article describes experimentation involving the effect of the relative positions of the 2 phases on the interfacial tension. Employing the systems of benzene and gelatin or sodium alginate, the results depended upon whether the drop formed in sissle drop procedure was formed from benzene or from solution. Although the experiments were performed utilizing the same solutions with the two systems side by side, the results obtained were consistently and appreciably different. The authors further suggest that the differences may be due to the structure of the solution itself.

THOMAS E. ARKINSON

ASPIRIN ANHYDRIDE

The Physical Chemical Evidence for Aspirin Anhydride as a Superior Form for the Oral Administration of Aspirin, Garrett, Edward R., J. Am. Pharm. Assoc., Sci. Ed. 48:676 (Dec.) 1959. (The Research Division, The Upjohn Co., Kalamazoo, Michigan)

The merits of aspirin anhydride are discussed relative to physical, chemical, and kinetic investigations indicating it to be a superior aspirin dosage form. The prime disadvantages of aspirin therapy, those of digestive upset and gastric mucosal irritation, are well known. The irritation may be due to (a) salicylic acid production, (b) the natural acidity of aspirin, or (c) the adhesion of undissolved acidic aspirin to the gastric mucosa. Aspirin anhydride was proved to be superior to aspirin in that (a) its salicylic acid production under pH conditions of the stomach or the intestine is neglible compared to aspirin, (b) aspirin anhydride is nonacidic, (c) aspirin anhydride has to dissolve to give aspirin which may be almost instantaneously absorbed into the blood so that the adhesion of irritating aspirin to the gastric mucosa cannot readily occur.

ROBERT P. MCMAHON

DETERMINATION OF FLAVONES

Quantitative Determination of Flavones in Citrus Bioflavonoids by Potassium Borohydride Reduction, Rowell, Kenneth M., Winter, Donald H., J. Am. Pharm. Assoc., Sci. Ed. 48:746 (Dec.) 1959. (Orange Products Division, Sunkist Growers, Ontario, Calif.)

Flavanones reduced with potassium borohydride and acidified with hydrochloric acid develop red to violet colors. This reaction forms the basis for a quantitative spectrophotometric method for the determination of flavones. The procedure outlined is sufficiently sensitive to determine quantitatively solubilized flavanones at concentrations of 0.02 mg./ml. Determinations of flavanone content of typical pharmaceutical formulations containing citrus bioflavonoids demonstrate complete recovery of added bioflavonoids. The method is rapid and the results are reproducible.

ROBERT P. MCMAHON

PREPARATION OF TABLETS FROM ACTIVATED COAL

Preparation of Tablets with Adsorptive Power from "Carbo Adsorbens," Balúch, J., Farmácia (Czechoslovakia) 29, 2:48 (Feb.) 1960. (Slovakofarma Works, Hlohovec, Czechoslovakia)

After investigating into the adsorptive power of various substances which should be taken into consideration when preparing adsorptive tablets from activated charcoal (the substances were studied in combination with activated charcoal), the author suggests the following composition as the best:

Activated Charcoal	0.25 Gm.
Powdered Saccharose	0.15 Gm.
Lactose	0.10 Gm.
Corn Wheat	0.10 Gm.

This blend (the weight data concern 1 tablet) is to be treated by the following binding liquid:

Tragacanth	0.02 Gm.
Bentonite	0.07 Gm.
Distilled Water	0.48 Gm.

The ready made granulate is tabletted in the dry state.

HUBERT ŽÁČEK

POSTGRADUATE STUDY OF PHARMACY IN CZECHOSLOVAKIA

Improving Erudition of Pharmacists, Lehký, M., Farmácia (Czechoslovakia) 29:40 (Feb.) 1960 (Slovak Institute for Postgraduate Study of Physicians, Pharmacy Department)

There are two institutes in Czechoslovakia educating pharmacists after diploma: the Czech institute in Prague and the Slovak one in Trenčín. Actually both are departments of pertinent institutes of postgraduate study for physicians. It is planned to specialize pharmacists in the following four disciplines: general pharmacy, pharmaceutical technology, pharmaceutical analysis, and medicinal plants. One of the main tasks of departments for postgraduate study of pharmacists is to be the education of the so-called "district pharmacists" (public officials inspecting all pharmacies in one district). Various monothematic or polythematic courses for many pharmacists have been arranged.

HUBERT ŽÁČEK

FUNGISTATIC AGENTS

The Preparation and Evaluation of Some Phenolic Ethers as Antifungal Agents, Coates, L. V., Drain, D. J., Macrae, F. J., and Tattersall, K., J. Pharm. and Pharmacol. 11(Suppl.):240T (Dec.) 1959. (Smith and Nephew Research Limited, Hunsdon Laboratories, Ware, Herts.)

A series of phenolic ethers, derivatives of hydroxybenzoic acids, benzaldehydes and acylophenones have been prepared and tested for antifungal action. The highest activity was found in those compounds having an amyloxy group ortho to a carbonyl radical. Experience with earlier tests led to the conclusion that therapeutic effect should not be assessed at one time only, for infection has three phases: an initial inflammatory phase, then a period when isolation of the fungus is readily accomplished, which is followed by regression of infection, and hair regrowth. The duration of the inflammatory phase was markedly shortened by water-in-oil emulsion, and polyethylene glycol based preparations of 2-n-amyloxybenzamide and 2-n-amyloxyacetophenone. The same ingredients in an alcoholic gel base, although showing little effect on the inflammatory phase, nevertheless considerably reduce the number of positive cultures and the time necessary for hair regrowth. These results, together with the low toxicity of the active ingredients and their lack of sensitizing or irritant properties, suggested that suitable formulations of these compounds might be of value in the treatment of human dermatophyte infections.

JAMES W. STOVER

DRUG CONTROL

Safe New Drugs and Their Control Under Law, Kessenich, W. H., Clinical Pharmacol. Therap. 1:53 (Jan.-Feb.) 1960. (Food and Drug Administration, Department of Health, Education and Welfare, Washington, D.C.)

The Food and Drug Administration's methods in evaluating new drugs is reviewed briefly to provide a better understanding of the role and function of the Food and Drug Administration in its regulation of new drugs. The physician can use new drugs with the confidence and assurance that studies have already been made which have verified the drug as safe. Governmental review has provided labeling which is available to the physician giving him all the essential information needed by him to use the drug safely. Food and Drug review does not constitute licensing nor is it an approval of the claims of efficacy. It does not mean, either, that the Food and Drug Administration is dictating how the physician should practice medicine or what drug is best for any particular patient. It simply implies that the physician has available to him information gained by the experience of his colleagues and reflected in the brochure to use in reaching his decision as to whether or not to use a drug.

DAVID BURKHOLDER

GOALS OF CLINICAL INVESTIGATION

Changing Trends in Clinical Investigation, Burnett, C. H., AMA Arch. Int. Med. 104:848 (Dec.) 1959. (Chapel Hill, N.C.)

Although this is an era in which the potential for the further development of experimental medicine and therapeutics is the greatest in history, the full exploitation of this potential will require solution of many problems. Reference is made to the place of animal experimentation in clinical investigation. From one point of view, it could be argued that the clinical investigator should limit his activities to the study of sick people and attempt to persuade his colleagues in the basic sciences to carry out the animal experiments. In practice this is impractical and is strongly opposed by the author for several reasons. First, such a policy is opposed to scientific principle. Second, society has become increasingly concerned with the perplexity of the legal, ethical, and moral aspects of human experimentation since the events of World War II. Third, many questions originating at the bedside can be more quickly and accurately answered, at least as applied to the animal species used, by carefully planned and controlled animal experiments than by study of the patient. Some experiments on humans are completely impossible; in others they are indecisive, and in many there is anxiety over the degree of hazard to the patients under study. It seems certain that clinical investigation should and will become more closely associated with the rapid developments in all the basic sciences. This prediction, however, carries with it certain implications as far as clinical research is concerned. The clinical investigator should remind himself periodically that his primary goals are related to the better understanding and treatment of sick people. The approach is less important than the goal.

DAVID BURKHOLDER

PARENTERAL METHODS

Parenteral Teaching—Practical and Philosophic Considerations, Sprowls, J. B., Bulletin of the Parenteral Drug Association, 14:2 (Jan.-Feb.) 1960 (College of Pharmacy, Temple University, Philadelphia)

An analysis of the knowledge and technics which enter into the conception, manufacture and control of reliable parenteral products reveals that specific curricula which would fulfill the requirements for this program have not been developed. However, students who have received their bachelor of science degree in pharmacy will have sufficient understanding of the important principles that, with comparatively little additional training, they should be capable of giving outstanding service, if not actual leadership, to the field. Graduates of other disciplines, such as bacteriology are also capable of making outstanding contributions to this work.

Collegiate education in this country is not directed to specific duties in which a student may become engaged after graduation, but at general areas of subject matter. After receiving his degree, the graduate specializes by entering his chosen area of work or by entering graduate studies. It would be inconsistent to offer training in a specialty before basic studies are completed and thereby run the risk of omitting some fundamental area of instruction. Therefore, serious training in parenteral work must be accomplished through graduate studies.

A graduate curriculum, to meet the needs of the parenteral manufacturing industry, would include the following areas of study: physical chemistry, product

formulation and stabilization, bacterial physiology, quality control (statistics), parenteral manufacturing, and research.

This is an attempt to outline the area of knowledge a person should possess if he is to exercise over-all supervision of the entire phase of operation. Many of the courses which are fundamental to other areas of work are equally fundamental for parenteral work. Cooperation with the bacteriology department and other departments is essential for providing the course work to prepare one for service in the parenteral field.

The author believes that schools of pharmacy have not felt a clear challenge for the development of such curricula. Many schools are adequately equipped to do so and would undoubtedly arrange such programs upon request.

W. F. BERTZ

CHLOROFORM

The Reaction of Bases with Chloroform, Coomber, D. I. and Rose, B. A., J. Pharm. Pharmacol. 11:703 (Nov.) 1959.

A previously presented article is discussed with reference to the reaction of certain bases with chloroform—presumably from impurities such as methylene halides. There was some doubt whether the bases would react with chloroform free of these impurities. The authors refluxed strychnine with chloroform free of methylene halide contaminants and obtained positive results. They conclude that strychnine does not react with pure chloroform. The use of chloroform made from the action of bleaching powder on acetone is advocated for the analysis of organic bases, rather than that made by the chlorination of methane or reduction of carbon tetrachloride.

J. OLIVER

BACTERICIDES IN BUFFER SOLUTIONS

Comparative Efficacy of Bacteriocidal Compounds in Buffer Solutions Part I, Hess, H. and Speiser, P., J. Pharm Pharmacol. 11:650 (Nov.) 1959.

A newer and more efficacious method of counting organisms previously exposed to bacteriocidal compounds is discussed. The newer membrane filter method presents the following advantages: (1) Any quantity of test mixture can be filtered; (2) the filters may be washed to eliminate the danger of bacteriostat carry-over; (3) colony growth occurs under uniform aerobic conditions; (4) an apparent greater sensitivity with comparatively small numbers of cells; and (5) the danger of heat bacteriostasis is excluded because no heat is used.

J. OLIVER

BACTERICIDES IN BUFFER SOLUTIONS

Comparative Efficacy of Bacteriocidal Compounds in Buffer Solutions, Part II, Hess, H. and Speiser, P., J. Pharm. Pharmacol. 11:694 (Nov.) 1959.

Various bacteriocidal compounds, including phenols, aromatic alcohols, organic mercury compounds, and quaternary ammonium compounds have been tested to relate the antibacterial action with the pH of the medium. Both gram-positive and gram-negative organisms were used. The phenols and alcohols showed greatest effect against gram-positive cells in an acid pH, whereas the gram-negative cells demonstrated a lower survival rate in a slightly alkaline medium (pH 8.5). Phenyl mercuric borate was more effective in an alkaline solution, thiomersal in acid solution. 4-Chloro-B-phenylethyl alcohol yielded promising results as a new bacteriocidal agent.

J. OLIVER

ANALYSIS OF RESERPINE

Analytical Methods for Recinnamine, Missan, S., Ciaccio, L., McMullen, W., Pazdera, H., and Grenfell, T., J. Am. Pharm. Assoc., Sci. Ed., 49:7 (Jan.) 1960. (Analytical Laboratories, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.)

The article describes several methods for the analysis of the pure compound mixtures of reserpine and recinnamine and pharmaceutical preparations. Four methods are described, *viz.*, ultraviolet absorbance, fluorometric methods, and a bromination method. Although all methods described are equally valid for pure recinnamine, the method of choice for crude rauwolfia preparations as well as bulk recinnamine is the ultraviolet method. The method of choice in tablet assay is the fluorometric method after oxidation with sodium nitrite. The bromination method is not valid for elixirs because of the very small amount of recinnamine present.

THOMAS E. ARKINSON

AMORPHOUS ALOIN

The Characterisation of Crystalline and Amorphous Aloin, Lister, R. E. and Pride, R. R. A., J. Pharm. and Pharmacol., 11:278T (Dec.) 1959. (Research Department, J. F. Macfarlan & Co. Ltd., Edinburgh, 8.)

Evidence is presented to show the marked differences between amorphous aloin and aloin as described in the *British Pharmacopoeia*, 1953. The first point of difference is, obviously, the amorphous nature of the material. The second is the high water-solubility. The two forms can further be distinguished by differences in the ultraviolet absorption spectra or paper chromatograms. Finally it was demonstrated that the amorphous type of aloin is a heterogenous substance, low in barbaloin content comprising the main water-soluble constituents of Cape aloes. Biological assay has shown that the potency of the amorphous aloin is about one-third that of aloin, B.P. A recommendation is made that it would be advantageous to have a test incorporated in official publications to differentiate crystalline aloin from the relatively impure and less active amorphous aloin.

ROBERT P. MCMAHON

ANTIBACTERIAL ACTION OF OXINE

Metallic Cations and the Antibacterial Action of Oxine, Beckett, A. H., Dar, R. N., and Robinson, Ann E., J. Pharm. and Pharmacol. 11:195T (Dec.) 1959. (School of Pharmacy, Chelsea College of Science and Technology, Manresa Road, London, S. W. 3)

The binding of cobaltous and manganous ions by *Staphlococcus aureus* suspensions, alone and in combination with oxine and with iron, was examined as part of a study of the mechanism of antibacterial action of oxine. The concentration of metal ions remaining in solution after contact with the bacterial suspensions was determined colorimetrically. The extent of iron, cobalt, and manganese ion binding by *Staph. aureus* suspensions was independent of the contact time between 20 and 60 minutes; binding was at least 90% complete within two minutes. Slight potentiation of metal binding by *Staph. aureus* was effected by the addition of a small proportion of oxine to the contact solutions. However, solutions containing equimolar proportions of oxine and either cobalt or manganese were devoid of activity.

ROBERT P. MCMAHON

DETERGENTS

Detergents and Detergency, Raphael, L., Mfr. Chemist 30:459 (Nov.) 1959.

Analysis shows that many of the well-known detergent powders contain 20 to 30% alkylaryl-sulfonate, up to 9% perborate and 25 to 35% phosphate. Perborate is an effective bleach above 140° F. for removing tea or coffee stains, but it may alter the color of woolens if used carelessly. Optical brighteners, if used in excess, can cause a bluish tint on the fabric. Liquid detergents mostly contain non-ionic and anionic surfactants. None of the liquids listed appear to be heavy duty products. The advantages of syndets (synthetic detergents) over soap in hard-water areas are well known. In soft water, built syndets are as successful as soap in washing fabrics and in general the report recommends their use. The effects of all types of detergents on textile fibers is similar. Discoloration of all textiles except cellulose acetate was observed, but the strengths of nylon and terylene were not reduced after several washings. While foam is a useful guide for active concentration of soap, this is not so for syndets. As regards the dermatitic effect of syndets, the report states that there is no evidence that they are any more harmful than soap. Prolonged use may make the skin very dry and cause cracks, allowing bacteria to enter.

DAVID BURKHOLDER

DETERMINATION OF SACCHARIN

The Determination of Saccharin, Parikh, P. M. and Mukherji, S. P., Analyst 85:25 (Jan.) 1960. (Zandu Pharmaceutical Works Ltd., Bombay 28, India)

Saccharin, being an imide, can be quantitatively precipitated as its silver salt from solutions at pH values below 6.0, and this fact has been used in evolving a simple and rapid volumetric method for determining saccharin and its preparations—sodium saccharin, elixir saccharin and tablet saccharin. Sodium hydrogen carbonate and sodium cyclamate, if present, do not interfere; interference from chloride is easily overcome by a slight modification of the method. The results are reproducible within a narrow range and similar to those obtained by standard methods.

DAVID BURKHOLDER

DEXTROSULPHENIDOL

Colorimetric Determination of Dextrosulphenidol and Raceophenidol, McChesney, E., Shekosky, J., Eckert, H., and Koss, R., J. Am. Pharm. Assoc., Sci. Ed., 49:28 (Jan.) 1960. (Sterling-Winthrop Research Institute, Rensselaer, N. Y.)

Bacteriologically, dextrosulphenidol is a potent chemotherapeutic agent. Obviously, knowledge of the absorption, distribution and excretion of the compound could be enlarged greatly if a method of chemical analysis were available. The authors describe studies undertaken in the colorimetric determination of dextrosulphenidol and its corresponding racemate, raceophenidol. Both compounds are degradated by alkaline hydrolysis, followed by periodate oxidation to form p-methylsulfonylbenzaldehyde, which can be determined colorimetrically as the alkali salt of its p-nitrophenylhydrazone. The authors describe analytical procedures for the determination of both compounds in blood plasma or serum, urine, feces, tissues, eggs, and poultry feed, based on these reactions. Recovery from the materials studied ranges from 70 - 100%. The least amount of either compound which can be determined satisfactorily is 1 microgram.

THOMAS E. ARKINSON

INTERFACIAL FILMS

Interfacial Films Between Benzene and Solutions of Salts of Arabic Acid, Shotton, E. and Wibberley, K., J. Pharm. Pharmacol. 11(Suppl.):120T (Dec.) 1959 (Department of Pharmaceutics, School of Pharmacy, University of London. Brunswick Square, W.C.1.)

Results of the determination of the interfacial tension between benzene and solutions of crude acacia, arabic acid, calcium arabate and magnesium arabate are summarized. All the materials showed similar behavior. With solutions of 1% w/v and over, the interfacial tension falls rapidly for a period of about 8 hours and then the rate of decrease becomes very much slower. At 96 hours equilibrium has not been attained. A tenacious film is formed in a few seconds and continues to increase in thickness with time. The evidence suggests that the film eventually formed is a substantial multilayer with many of the properties of the elastic solid. A film of this kind would account for the stability of acacia emulsions.

JAMES W. STOVER

STERILITY TESTING

A Note of the Use of Membrane Filters in Sterility Testing, Sykes, G. and Hooper, M. C., J. Pharm. Pharmacol. 11(Suppl.)-:235T (Dec.) 1959. (Microbiology Department, Boots Pure Drug Co. Ltd., Nottingham, England.)

Filtration techniques have been applied advantageously in testing antibiotics and certain other medicaments, including oily solutions, for sterility. A known volume is filtered through a single membrane and then the membrane is cultured either on the surface of a prepared nutrient agar plate or by immersion in a liquid nutrient medium. The principal advantage is that having filtered the sample, the membrane can be washed free from any inhibitory or interfering substances in the original solution. Further advantage is the frequent elimination of the necessity for subsequent subculturing of oils and oily solutions which cause some cloudy precipitation in the medium and so mask any bacterial growth which may have taken place. A disadvantage is that it requires skill in aseptic handling and a sterile room with suitable aseptic screen, or better still the sealed screen technique should be employed. Low recoveries have also been reported in some instances with phenol-damaged organisms.

JAMES W. STOVER

INACTIVATION OF QUATS

A Study of Factors Affecting the Inactivation of Quarternary Ammonium Compounds on Agar, Groves, M. J. and Turner, H. A., J. Pharm. and Pharmacol. 11:169T (Dec.) 1959. (Department of Pharmacy, University of Nottingham.)

This study was concentrated on factors affecting the development of inhibition zones by quarternary ammonium compounds on seeded agar plates. Experimentation was centered around theories attributing the reduced activity to a slow rate of diffusion owing to the high molecular weights of quarternary ammonium compounds. By the use of a dye, the diffusion rate was verified, and the results disprove any diffusion theory of inactivation leaving this "resistant" property of agar on quarternary ammonium compounds open for further investigation.

ROBERT P. MCMAHON

CLOSURES

Practical Problems in Closures, Portner, P. E., Bulletin of the Parenteral Drug Association, 14:7 (Jan.-Feb.) 1960. (Wyeth Laboratories Inc., Marietta, Pa.)

The problems on closures have been brought to focus only in recent years by the pharmaceutical industry. Diversification in the use of closures today presents a multitude of conditions difficult to satisfy. One particular closure may be well suited for one preparation, but may be completely unsatisfactory for another preparation. Most of the efforts within the pharmaceutical industry in the past 15 years have been unsuccessful. Within the closure industry, most of the operations are in keeping with the fact that rubber technology is more of an art than a science.

It is interesting to note that the USP XII edition states that caps or stoppers used for closing containers are to be made from a good quality material. Thirteen years later, in 1955, the USP XV simply stated that the closure is a part of the container. This indicates the failure of industry to make acceptable standards sufficient for official recognition. It is well known that more reactions occur between the rubber closure and the injection than there are reactions between the glass container and like solutions. With this in mind, it is interesting to note that the USP XV devotes 4 pages of its text to the standardization of glass containers and only eight words relative to closures.

Part of the problem of the closure industry arises from the processing to which the rubber is subjected. Supposedly identical formulations processed and cured in the same manner will give rise to different compatibilities due to some slight variation between batches. To make the closure industry a systemized science, we must define methods, ingredients, machinery, and even men. The impracticality of this approach is self evident.

The British standards institution circulated recently to all concerned in the closure industry a tentative standards draft for review. In the testing procedure, closures are sealed in vials with the test solution. The vials are exposed to temperatures from 4° C. to 50° C. or higher for 3 to 12 months. Inspection is made at 1 month, 3 months and every third month thereafter. A control consists of vials containing an identical solution with previously tested closures that proved satisfactory. The vials are inspected at the stated times for foreign insoluble matter, haze and development of color. Tests for potency, toxicity, etc. are carried out at the same time.

The closures that pass this test no doubt will prove satisfactory. Note, too, that this test terminated after more than 1 year of elapsed time. The industry cannot apply this test routinely because of the excessive inventories and associated problems.

Experience by one company during the past 5 years has resulted in tests of shorter duration than that described. A representative sample is processed and sterilized like a production lot. The closures are placed directly in a number of biological and pharmaceutical solutions contained in screw capped test tubes. They are exposed for 7 days at 5° C., 25° C. and 37° C. At the end of the test period an examination is made for clarity, color changes, precipitation and changes on the surface of the closure.

It is not uncommon to find differences in the compatibilities of closures of presumably identical formulation and curing. Closures that exhibit incompatibilities are restricted to use with products with which it had not reacted. Thus, certain shipments of closures can be used which would otherwise be rejected.

The problem of coring of rubber closures is perhaps the most controversial problem in the industry. Part of the problem is related to the physical characteristics of the closure. Factors in processing and manufacturing of the closure may be involved. The incidence of coring also varies with the size of the needle. As the size of the needle increases, the coring incidence decreases.

The author recommends that the closure manufacturing industry organize a group among themselves in order to study and share in the solution of their mutual problems.

W. B. BERTZ

AIR FILTRATION

Filtration of Air Supply to Sterile Filling Room, Baker, A. K., Bulletin of the Parenteral Drug Association, 14:8 (Jan.-Feb.) 1960. (The Baker Co. Inc., Biddenford, Maine)

The fundamental problems of filtering and supplying superclean air are much the same for the pharmaceutical industry as it is for the instrument manufacturing industry. Because of the exigencies of our defense program, extensive developments are being made in this field.

A filtering system for a dust controlled area will contain not less than 2 types of filters in series and may contain as many as 5 elements. The first stage will usually be a glass wool filter. The second stage can be an electrostatic precipitator or a high efficiency mechanical type which will remove 80-90% of the airborne dirt. The third stage, which is sometimes the final stage, when the second stage is omitted, consists usually of an "absolute" type of filter with an efficiency of 99.95% and which will effectively remove particles down to 0.3 micron in diameter. A fourth stage, using activated charcoal is sometimes added ahead of the final filter to remove gaseous air contaminants. The fifth section might be a bank of ultraviolet lamps within the air duct.

The air ducts, following the last stage of filtering, are of utmost importance. Stainless steel of the 300 series is the most acceptable material for the construction of the air ducts. Likewise, this material is best suited for the construction of the walls and work bench areas in the dust controlled room.

The dust controlled room is designed to eliminate anything which may generate dust within the control area. Likewise, the unit is designed to eliminate dust being brought into the area. Entrance is gained through airlocks. Air showers, similar to water showers, are used to remove dust. Technicians are required to wear special headgear, clothing, and bootees to limit dust. Materials brought into the area are treated with similar precautions to control dust.

An important facet that cannot be neglected is the training of employees to make them conscious at all times of the role they play in the dust control program. A "hospital type" psychology must be instilled in the workers so that the neatness of the environment "catches on" with them.

Another approach to a dust controlled environment which will suffice for many purposes is the use of a pressurized enclosed workbench known as the sterishield. This versatile unit eliminates much of the accessory equipment required for a dust controlled room. This unit has literally no limit in size and may be adopted to almost any process.

W. F. Bertz

ASPIRIN ANHYDRIDE

Stability, Products, and Mechanism in the Pyrolytic Degradation of Aspirin Anhydride, Garrett, Edward R., Schumann, Edward L., Grostic, Marvin F., J. Am. Pharm. Assoc., Sci. Ed. 48:684 (Dec.) 1959. (The Research Division, The Upjohn Co., Kalamazoo, Michigan)

The effects of crystallizing solvent and moisture on the pyrolytic degradation of aspirin anhydride were studied by infrared spectroscopy. The unexpected effects of "soft glass"-catalyzed surface decomposition were observed. Micronization, drying, and avoidance of contact with alkali increased the thermal stability. A mechanism of acyl transfer in the formed melt adequately explains the products identified by isolation and infrared studies. In moist systems the end products of the pyrolysis of aspirin anhydride are acetylsalicoylsalicylic acid and acetic acid. In anhydrous systems the mixed and symmetrical anhydrides of these two acids are the major products.

Robert P. McMahon

OUTLOOK FOR COLD STERILIZATION

Radiation Sterilisation of Pharmaceuticals, Powell, D. B., Mfr. Chemist 30:435 (Nov.) 1959.

The prospect of an irradiation sterilization plant being available soon to British industry has renewed the interest in sterilizing pharmaceutical and medical products by gamma rays. One of the first commercial applications found for atomic radiation is the sterilizing of packed surgical catgut sutures. A five-year development project by Ethicon Inc. in the United States has showed that while radiation is more expensive than heat treatment, a better product is obtained. The author working at Wantage, England, where the new irradiation plant is being built, clarifies current authoritative thinking on gamma ray sterilization of pharmaceuticals and hints at the views likely to be put forth in the special report expected from the Association of British Pharmaceutical Industry. Cobalt 60 gamma rays or any other gamma rays of similar or lower energy will not produce residual radioactivity. Gamma radiation provides a new, safe and effective means of carrying out sterilization of a wide variety of materials and its adoption is likely to be widespread in the immediate future.

David Burkholder

PENETRATION OF SURFACE ACTIVE AGENTS INTO SKIN

Penetration of Sodium Laurate and Sodium Dodecyl Sulfate into Excised Human Skin, Blank, Irvin H. and Gould, Edith, J. Investig. Derm. 33:327 (Dec.) 1959. (Dermatological Research Laboratories of the Department of Dermatology, Harvard Medical School, at the Massachusetts General Hospital, Boston, Mass.)

Simple dryness of the skin can result if a substance penetrates into the stratum corneum only. Irritations more severe can occur only if a substance penetrates the major barrier of the skin and reaches the viable cells of the epidermis. Therefore, this study was undertaken to determine the penetration of various anionic surfactants (constituents of soaps and household cleaners) into the different layers of the skin and the factors which affect this penetration.

In this study the sodium salt of dodecyl sulfate (a representative alkyl sulfate) has been compared with sodium laurate. Sodium dodecyl sulfate is thought to be more irritating than the sodium salts of other alkyl sulfates. Sodium laurate and sodium dodecyl sulfate were chosen for investigation because the size and shape of their molecules are similar and because each can be obtained in relatively pure form and can be synthesized with a radioactive element.

From weak, unbuffered, mildly alkaline aqueous solutions, sodium laurate seems to be able to penetrate into the epidermis and dermis of excised human skin. From similar solutions, sodium dodecyl sulfate, on the other hand, appears to penetrate only in very small quantities below the barrier of normal undamaged skin and for the most part, to be retained in the stratum corneum. When in quite alkaline, buffered solutions (pH 10.5) both of these surfactants penetrate into the dermis. At this alkalinity the natural barrier is damaged.

David Burkholder

CURRENT LITERATURE

. . . also calling your attention to the following articles appearing in recent hospital and pharmaceutical journals

. . . . . .

ADMINISTRATION

—General

Carner, Donald C.: A New Concept in Hospital Pharmacies, *Tile and Till 46*:opp. 24 (Mar.-Apr.) 1960.

Heller, William: Annual Administrative Reviews: Pharmacy, *Hospitals 34*:125 (Apr. 16) 1960.

—Cost of Drugs

Provost, George P., and Heller, William M.: How Break-Even Pricing of Drugs Works, *Modern Hosp. 94*:122 (May) 1960.

—Dispensing

Eleazer, Robert B.: Emergency Drug Cabinet Helps Fill Night Orders, *Modern Hosp. 94*:146 (Apr.) 1960.

Safren, Miriam Aronstein, and Chapanis, Alphonse: A Critical Study of Hospital Medication Errors, *Hospitals 34*:32 (May 1) 1960.

—Personnel (Women in Pharmacy)

Anon: Women in Hospital Pharmacy, *Tile and Till 46*:opp. 24 (Mar.-Apr.) 1960.

LAWS AND LEGISLATION

Archambault, G. F.: Six Hospital Pharmacy Issues Seeking Solutions, *Hospitals 34*:81 (May 1) 1960.

NARCOTICS

Krantz, John C.: How to Cope With Drug Addiction in Hospitals, *Modern Hosp. 94*:66 (Feb.) 1960.

RESEARCH

Thomas, Girard W. T.: How to Select Colorimetry Instruments, *Modern Hosp. 94*:132 (Apr.) 1960.

SMALL HOSPITALS

Hauser, Louis: Pharmacy Fits Small Hospital Pattern, *Modern Hosp. 94*:116 (Mar.) 1960.

Kunkel, Frank: How One Retail Pharmacy Serves a Small Hospital, (Abstr.), *Hosp. Topics 38*:57 (May) 1960.

McNabb, Douglas M., and Wyatt, Roger E., Jr.: Hospital-Retail Pharmacy Cooperation: Close Look at a Working Agreement, *Hospitals 34*:50 (Mar. 1) 1960.

GENERAL

Zugich, John J.: Hospital Pharmacy Unanswered, *Am. Profess. Pharm. 26*:259 (Apr.) 1960.

DRUG EVALUATIONS

by the Council on Drugs of the American Medical Association

► THE FOLLOWING MONOGRAPHS and supplemental statements on drugs have been authorized by the Council on Drugs of the American Medical Association for publication and inclusion in *New and Nonofficial Drugs*. They are based upon the evaluation of available scientific data and reports of investigations.

The issue of the *Journal of the American Medical Association* from which each monograph has been taken is noted under each monograph. Monographs in this issue of the JOURNAL include those published in the *A.M.A. Journal* for March 5* and March 19, 1960.

Notice

New and Nonofficial Drugs 1960 is now available from your local bookstore and from the publishers, J. B. Lippincott Company, Philadelphia, Pa. This 1960 edition contains monographs of drugs evaluated by the Council on Drugs of the American Medical Association and published in the Journal of the A.M.A. to October 17, 1959. The indexes listed below contain those drugs evaluated and published between October 24, 1959 and March 19, 1960.*

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TO DRUGS EVALUATED IN THIS ISSUE

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TO EVALUATED DRUGS AND ARTICLES IN THE FEBRUARY, MARCH, APRIL AND MAY ISSUES OF THE AMERICAN JOURNAL OF HOSPITAL PHARMACY.

* Some monographs published in the March 5 issue of the *A.M.A. Journal* appeared in the May issue of This Journal.

The Council has authorized publication of the following report.

H. D. KAUTZ, M.D., *Secretary.*

This report, prepared by the Subcommittee on Breast and Genital Cancer, is the result of a 12-year collaborative undertaking to study the effect of androgen and estrogen therapy in the treatment of disseminated mammary cancer. As one of the earliest projects of this type, it has served to blaze a trail for a number of studies which have followed. It will undoubtedly serve as a base line for comparative evaluation of studies which are under way in the field of cancer. A great deal could be said about the devotion of the two men who originally headed the project and who have since died, namely, Drs. Ira T. Nathanson and Earl T. Engle. The enthusiasm and effort of the collaborators and the members of the subcommittee speak well for the participants. Credit should be given to those firms in the pharmaceutical industry which cooperated and so generously provided the products used by the investigation. The present members of the Subcommittee on Breast and Genital Cancer, headed by Dr. Ian Macdonald, are to be congratulated on their integrity and resolution in assuming the responsibility for the follow-up and reanalysis and in discharging their duties to the medical profession by assembling and interpreting the data from which this report is derived. Copies of the data and statistics used in preparing this report ("Accumulated Statistology") are available on request from the Secretary, Committee on Research.

NORMAN DE NOSAQUO, M. D.,
Secretary,
Committee on Research,

Androgens and Estrogens in the Treatment of Disseminated Mammary Carcinoma

RETROSPECTIVE STUDY OF NINE HUNDRED FORTY-FOUR PATIENTS

►IN THE FALL of 1947, the Therapeutic Trials Committee (later designated the Committee on Research) of the American Medical Association undertook the sponsorship of a cooperative investigation of the effects of steroid hormones in the treatment of advanced or disseminated carcinoma of the breast. This investigation was co-ordinated by a Subcommittee on Steroids in Cancer including Drs. Ira T. Nathanson (deceased), Frank E. Adair, Willard M. Allen, and Earl T. Engle (deceased). In 1956, the subcommittee was reconstituted and redesignated the Subcommittee on Breast and Genital Cancer. Members of the Subcommittee on Breast and Genital Cancer of the Committee on Research are Drs. Ian Macdonald (Chairman), Los Angeles; Alfred Gellhorn, New York; B. J. Kennedy, Minneapolis; and Samuel G. Taylor, III, Chicago. With the support of the Committee on Research, and especially of its chairman, Dr. Stuart Mudd, the subcommittee has brought to completion the study which started a decade ago. The material consists of pooled data contributed by the following 60 collaborating investigators, without whose original and continued co-operation this report would not have been possible: Drs. Paul D. Abramson, Frank E. Adair, T. J. Anglem, Lionel S. Auster, H. C. Ballon, R. W. Begg, Frederick Hardy Bowen, A. J. S. Bryant, William Y. Burton, Franz Buschke, L. R. Chauncey, R. L. Clark, William A. Cooper, A. R. Curreri, Charles Eckert, Lucille Ellison, George C. Escher, Louis A. Eshman, Barry Friedman, L. H. Garland, Leonard B. Goldman, L. W. Gorham, Robert C. Grauer, Robert B. Greenblatt, Charles B. Hanna, Margaret Hardie, Joseph A. Hepp, Roy Hertz, Robert Huseby, B. J. Kennedy, Morton Kligerman, Edwin A. Lawrence (deceased), George Q. Lee, Henry Lemon, Edward F. Lewison, Champ Lyons, Ian Macdonald, S. S. Marchbanks, E. Perry McCullagh, Barton McSwain, John M. Modlin, Paul J. Murison, Ira T. Nathanson, H. E. Nieburgs, Kenneth B. Olson, Robert J. Parsons, Karl E. Paschkis, R. W. Postlethwait, Rieva Rosh, W. C. Sealy, Reginald A. Shipley, Joseph Silverstein, Arthur G. Siwinski, James A. Stapleton, Augustus Street, Samuel G. Taylor, III, G. M. Tice, Keene M. Wallace, Grant E. Ward, and Benjamin B. Wells. The consultants in radiology included Drs. L. H. Garland and Leo G. Rigler. The consultants in pathology were Drs. Lauren V. Ackerman, Fred Stewart, and Arthur Purdy Stout. Dr. Stanley C. Harris served as consultant in biometrics.

At intervals, usually every two years, a conference of the collaborating investigators was held at the headquarters of the A. M. A. in Chicago. At the 1956 conference, the subcommittee determined the necessity of a complete reanalysis and recoding of the information which had been contributed concerning 1,983 patients. The successful completion of this laborious project was facilitated by Dr. Alex Sahagian-Edwards, College of Physicians and Surgeons, Columbia University and Francis Delafield Hospital, New York City, who served as Research Associate to the subcommittee for a 15-month period, 1956 to 1958.

Objectives of Study

The original objectives of this investigation, as established by the parent subcommittee, were outlined at the First Conference on Steroid Hormones and Mammary Cancer in Chicago, April 4-7, 1949.[1] It soon became apparent in a study of this magnitude that certain objectives could not be achieved practically or accurately. Specifically, some of the objectives were to establish which morphologic types of breast cancer were affected by androgen and estrogen therapy, the dosage necessary to achieve favorable effects, the duration of palliation, and the criteria by which improvement could be judged. Arrangements were made with the Armed Forces Institute of Pathology for a central registry, through which surgical and autopsy specimens could be reviewed by a group of consultants. Histological changes in

TABLE 1.—*Cases Submitted for Analysis*

Cases complying with criteria for inclusion in study:		
Androgen-treated	580	
Estrogen-treated	364	
Total accepted for study		944
Cases not complying with criteria for inclusion in study:		
Not mammary cancer	19	
Male breast cancer	2	
Information lacking	372	
Not disseminated disease	309	
Radiation-treated	105	
Castrations	69	
Combined treatment	25	
Not sex steroids	22	
Ancillary treatments	14	
Inadequate dosage	101	
Miscellaneous	1	
Total rejected from study		1,039
Total submitted for analysis		1,983

responsive cases were comparable to the effects of irradiation, in both epithelial and stromal elements. No histological criteria for recognition of responsive tumors were apparent, nor did these studies provide any explanation of the mechanism of hormonal action.[2] Serial roentgenograms submitted to the consultants in radiology were impossible to evaluate, due to variations in techniques. Effort directed toward the elucidation of hormonal action was considered impractical in a group study. Such areas as the metabolic aspects of hormonal therapy, cytochemical effects, and the morphologic and functional changes induced in various tissues were not investigated.

It was the current subcommittee's opinion that the data available were sufficient to allow the following analyses: (1) determination of the objective responses of the neoplasm to estrogenic and androgenic hormones when administered to women with disseminated mammary carcinoma, (2) comparison of the effectiveness of androgens and estrogens, (3) clarification of the criteria for selection of patients and indications for hormonal treatment by estrogens and androgens, and (4) elaboration of certain aspects of the natural history of the disease.

Methods and Materials

Reports of 1,983 patients with mammary carcinoma treated by steroidal hormones were submitted to the subcommittee by the 60 investigators. This report is concerned with 944 cases (table 1) which fulfilled the following criteria. 1. The diagnosis of mammary carcinoma was established histologically in every patient. 2. Unequivocal evidence of distant dissemination of the disease was present, which was unsuitable for radiotherapy or surgical palliation. Specifically, it was required that spread beyond the regional (axillary) nodes be demonstrable in multiple foci, or be of such extent in dominant areas that irradiation was impractical, or both. Each patient represented genuine, distant dissemination so advanced as to require a systemic approach in treatment. 3. The patient must not have been irradiated or castrated within the six-month period immediately preceding hormone therapy. This did not exclude patients with multiple lesions who received x-ray therapy to a single symptomatic area, unless such irradiation resulted in any possibility of ovarian exposure, e. g., treatment to lumbar spine and pelvis. 4. No more than one hormone was administered during a single period of observation. 5. The hormone was administered for at least one month. 6. The patient received hormones designated by the subcommittee, with dosages in reasonable accordance with established protocols. 7. A completed initial case report was submitted and was followed by progress reports at suitable intervals.

The material consisted of an initial case report of the patient, with historical data concerning (1) diagnosis and treatment of the primary disease, 2() menstrual history, (3) past illnesses and operations (4) treatment of metastases prior to admission to this study, (5) description of size and location of lesions as indicated on appropriate diagrams, and (6) specification of compound and dosage schedule to be employed. The progress reports provided the following information: (1) total dose of hormone, (2) duration of therapy, (3) reason for interruption or discontinuance of therapy, (4) general condition of patient, (5) objective changes observed in each lesion, (6) side-effects and other observations relevant to hormone therapy, and (7) date of death.

Despite the attempt to centralize pathological and roentgenographic interpretations, it was impractical to interpret these data. Therefore, the interpretation of the investigator and his own radiologist or pathologist was accepted as evidence for or against tumor regression.

In the evaluation of effectiveness of hormone treatment, only evidence of objective improvement was accepted as constituting reasonably satisfactory proof of a tumor-suppressive action. The definition of objective regression, which was rigidly adhered to in the following analysis, was stated as follows: a distinct, measurable decrease in one or more dominant metastatic areas by clinical or radiographic examination, without progression of any other metastatic lesions and with no new foci of disease having appeared. Indications of subjective improvement were ignored in this study of objective data; gain in weight, relief of pain, increase in feeling of well-being, improved blood chemistries, and improvement of hematopoiesis were not regarded as objective criteria. Patients classified as exhibiting "progression" included not only those with evidence of an increased extent in any lesion or lesions while under treatment but also those in whom the disease apparently remained stationary under therapy. The static cases numbered only 29.

The primary data concerning response and survival are based on the initial treatment of 944 patients. Calculations on survival were limited to patients treated by a single sex hormone, excluding those patients who subsequently received other steroid substances or who were subjected to endocrine ablative procedures. Two hundred eight patients subsequently received one or more courses of the same or another hormone. The response to these treatments is considered separately.

Androgen Series.—A total of 580 patients received androgen therapy as outlined in table 2. Although the majority of patients were treated in accordance with the dosage schedules outlined in this table, necessary variations in the individual management of patients not infrequently required changes from one schedule to another or, less often, some departure from the recommended protocol. For this reason, the criterion of adequate dosage is based in terms of total dosage. All patients in this group were treated for a minimum period of one month, according to one of the dosage schedules shown in table 2.

TABLE 2.—*Androgen Series*•

Patients, No.	Substance	Schedule of Dosage	Amount, Mg.	Frequency	Route of Administration
415	Testosterone propionate	A	25	3 times weekly	Intramuscular
		B	50	3 times weekly	Intramuscular
		C	100	3 times weekly	Intramuscular
		D	200	3 times weekly	Intramuscular
12	Testosterone cyclopentylpropionate		200	3 times weekly	Intramuscular
45	Stanolone		100	3 times weekly	Intramuscular
20	Methandriol		100	3 times weekly	Intramuscular
88	Methyltestosterone	A	100	Daily	Oral
		B	200	Daily	Oral
580					

• Standard of reference was testosterone propionate, 100 mg., 3 times weekly. Recommended dose of other agents in terms of estimated androgenic equivalents, as determined by an advisory panel.

Estrogen Series.—A total of 364 patients were treated with estrogenic steroids as shown in table 3, for a minimum period of one month.

Follow-up: The clinical course of 844 patients (89.4%) was followed from the beginning of steroid treatment until time of death or the time of analysis. Of the 580 androgen-treated patients, 516 (89.0%) were followed to time of death or were still alive at the time of analysis; of the 364 estrogen-treated patients, 328 (90.1%) were followed to time of death or were still alive at the time of analysis.

Results

Androgen Series.—The frequency of tumor regression among the 580 androgen-treated patients was 21.4%. The distribution of these patients by age at the time of starting hormone therapy is shown in figure 1. Due to the recommendation of the sub-committee that estrogens be avoided

TABLE 3.—*Estrogen Series**

Patients, No.	Substance	Schedule of Dosage: Amount, Mg.	Schedule of Dosage: Frequency	Route of Administration
155	Diethylstilbestrol	15	Daily	Oral
62	Ethinyl estradiol	3	Daily	Oral
57	Chlorotrianisene	24	Daily	Oral
29	Conjugated estrogenic substances	30	Daily	Oral
25	Dienestrol	15	Daily	Oral
21	Diethylstilbestrol dimethyl ether	30	Daily	Oral
15	Estradiol dipropionate	5	2 times weekly	Intramuscular
364				

* Standard of reference is diethylstilbestrol, 15 mg. daily. Recommended dose of other agents in terms of estimated estrogenic equivalents, as determined by an advisory panel.

in the treatment of premenopausal women, the prevalence of younger women among those receiving androgen treatment is conspicuous. There were 160 premenopausal patients in this group, of whom 32 (20.0%) manifested objective regression. Objective regression was recorded for 92 (21.9%) of the 420 postmenopausal, androgen-treated patients. Within the postclimacteric group, menopause occurred naturally in 277, was induced in 104, and was of undetermined nature in 39 patients. (All reference to patients being premenopausal or postmenopausal indicates their status at the start of hormonal therapy. The term "induced menopause" refers

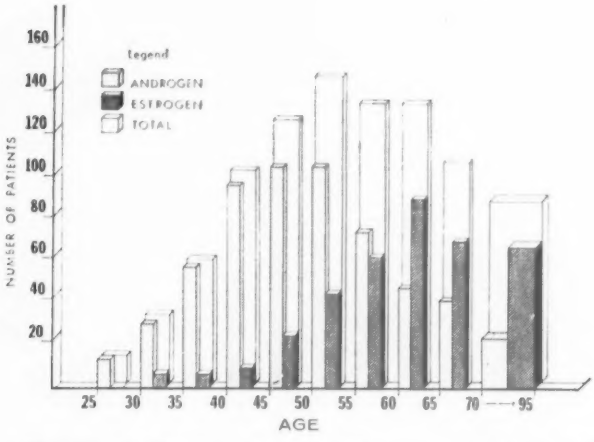

Fig. 1.—Distribution of patients by age at treatment of metastases.

to patients who had oophorectomy or castration by irradiation prior to the beginning of hormone therapy, whether related or unrelated to treatment of the primary carcinoma.)

The incidence of tumor regression was correlated with treatment beginning during successive 4-year intervals after the menopause through 16 years, and for those 17 or more years postmenopausal (table 4, fig. 2). The numerically largest group treated by androgens was in the immediate postmenopausal period of zero through four years. It is evident that nine or more years after the menopause there is an increased probability of obtaining an improvement with androgenic therapy ($x^2 = 6.65$, $p < 0.01$). This correlation of regression frequency with increasing postmenopausal interval is confirmed by a significant ($p < 0.01$) "r_pb." (Whenever applicable, statistical methods have been used as an aid in the interpretation of results. Statistical significance is expressed in terms of probabilities that observed differences are due to chance. The smaller the "p" values, the less likely that observed differencs may be attributed to coincidence. Thus, $p < 0.05$ means that less than 5 times in 100 would a difference be attributed to chance; $p < 0.01$ is less than 1 in 100. Conventionally, the rigid

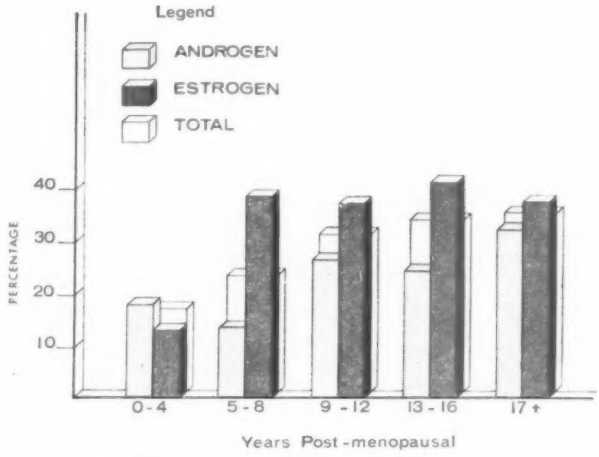

Fig. 2.—Frequency of regression by interval from menopause to treatment of metastases, shown as percentage within each 4-year group.

minimum requirement for significance is $p < 0.01$, though a less critical but acceptable level of confidence is $p < 0.05$. For those interested, statistical procedures [and their symbols] which have been applied to the data in this study are: "r," correlation of quantitative data; "r_pb" (point biserial), correlation of dichotomous values with quantitative values; "t" ratios, comparison of quantitative values; chi square, comparison of qualitative values. In every instance of chi square application, the correction for continuity has been included.)

An evaluation of frequency of regression according to anatomic sites was attempted. Comparison of the effectiveness of androgens on metastatic involvement in peripheral soft tissue, viscera, and bone for all cases showed no significant differences (table 5). An evaluation of effectiveness on involvement of multiple system (e. g., viscera and bone, soft tissue and bone) was not practicable.

TABLE 4.—*Incidence of Regressions Correlated with Interval Between Menopause and Beginning Hormone Therapy*

Interval Between Menopause and Hormone Therapy, Yr.	Patients, No.	Androgen: Patients Treated, No.	Androgen: Regressions: Patients, No.	Androgen: Regressions: %	Estrogen: Patients Treated, No.	Estrogen: Regressions: Patients, No.	Estrogen: Regressions: %	p*	χ^2
0-4†	186	154	27	17.5	32	4	12.5	>0.1	0.189
5-8	103	61	8	13.1	42	16	38.0	<0.01	7.356
9-12	125	68	18	26.5	57	21	36.8	>0.1	1.112
13-16	92	38	9	23.7	54	22	40.7	>0.1	2.191
17+	185	60	19	31.7	125	46	36.8	>0.1	0.271
Premenopausal	167	160	32	20.0	7	...	...	...	...
Unknown	86	39	11	28.2	47	25	53.2	<0.05	4.489
Total	944	580	124	...	364	134	...	...	...

* As applied here, "p" means the probability that differences between percentage regression with androgens and estrogens are due to coincidence.
† Each time interval is inclusive, e. g., from 0 through the entire 4th year = 0-4 yr.

TABLE 5.—*Correlation of Incidence of Regression and Location of Metastases*

Menopause Status	Site*	Androgen: Patients, No.	Androgen: Regression, No.	Androgen: Regression, %	Estrogen: Patients, No.	Estrogen: Regression, No.	Estrogen: Regression, %
All cases	Soft tissue	69	16	23.2	98	37	37.8
	Viscera	35	10	28.6	35	14	40.0
	Bone	162	39	24.1	33	9	27.3
Postmenopausal (natural)	Soft tissue	33	6	18.2	81	33	40.7
	Viscera	10	3	30.0	25	8	32.0
	Bone	80	25	31.3	23	7	30.4
Premenopausal	Soft tissue	21	4	19.0	...	...	...
	Viscera	17	5	29.4	...	...	...
	Bone	39	7	17.9	...	...	...

* Dissemination limited to these sites; cases with involvement of multiple systems excluded.

The average duration of life for all 427 patients receiving androgens as the only form of steroid therapy, and followed to time of death, was 11.4±9.9 months from institution of treatment. This period of average longevity was 19.1 ±12.2 months for those patients who demonstrated regressions and only 9.7±8.4 months in the nonresponsive patients ($t=8.14$, $p<0.01$). The average duration of survival of groups divided by menopausal status, primary treatment status, and responsiveness is presented in table 6. Longer survival associated with regressions is again demonstrated.

When the androgen-treated, naturally postmenopausal patients were grouped into responsive and nonresponsive groups, and the percentage of the sample still alive at selected intervals after beginning hormone therapy was graphed (fig. 3), a significantly greater ($p<0.001$) proportion of responders was found to be alive for periods up to 48 months.

TABLE 6.—*Comparison of Average Duration of Survival of Responders and Nonresponders*

Treatment	Ovarian Status	Status of Primary Lesion	Regression: Patients, No.	Regression: Average Survival, Mo.*	Non-regression: Patients, No.	Non-regression: Average Survival, Mo.	p
Androgens	Premenopausal	Untreated	5	24	18	7	<0.001
		Treated	15	17	82	11	<0.07
		Av.	...	18	...	11	...
Androgens	Postmenopausal (natural)	Untreated	8	16	31	9	<0.05
		Treated	32	21	123	10	<0.001
		Av.	...	20	...	10	...
Estrogens	Postmenopausal (natural)	Untreated	26	20	40	8	<0.001
		Treated	45	31	87	12	<0.001
		Av.	...	27	...	11	...

* After start of hormone therapy.

Estrogen Series.—The frequency of regressions among 364 patients treated by various estrogens was 36.8%. This calculation included seven premenopausal patients, in all of whom progression of the neoplastic lesion was noted. Figure 1 demonstrates that the group treated with estrogens was comprised of chronologically older women (average age, 63 years) than the androgen-treated group (average age, 51 years).

Menopause occurred naturally in 294 cases, was induced in 16, and of undetermined type in 47. The menopause of 236 of 310 patients (table 7) occurred nine or more years before institution of estrogen therapy for metastatic disease. The regression rate of this group (37.7%) was not significantly higher than that of the group with recurrence at an earlier postmenopausal phase (27.0%). However, when the group was made more homogeneous by excluding patients whose primary lesions were untreated, or had occurred premenopausally, the r_pb is significant ($p<0.05$), indicating an increase in rate of regression as the time between institution of hormonal treatment and the menopause becomes longer.

The average duration of life for all 243 cases receiving estrogens as the initial and only form of steroid therapy was

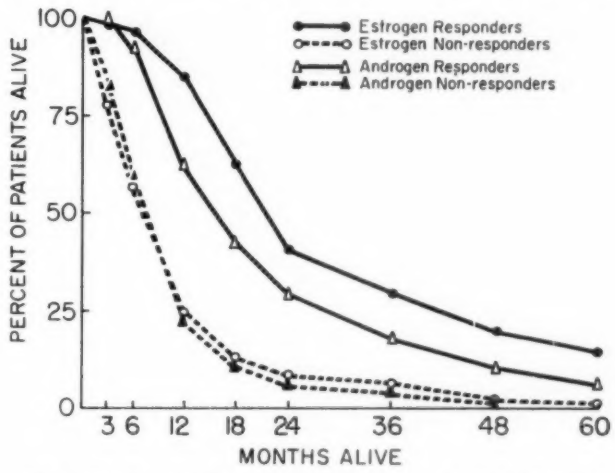

Fig. 3.—Comparative survival curves of natural postmenopausal patients from initial treatment of metastases.

16.5±16.1 months from institution of therapy (table 8). This period of average longevity was 27.3±18.2 months for those who manifested regressions and only 10.4±10.8 months for the unresponsive patients ($t=9.08$, $p<0.001$). Table 6 presents, for those women who had a natural menopause, the average months of survival after beginning hormone therapy, according to their response to treatment. Again it is obvious that patients in whom the disease regressed had a significantly longer period of survival than did those who failed to improve. In a survival curve (fig. 3), the proportion of patients alive in each period through 48 months after beginning hormone therapy was very significantly greater ($p<0.001$) for responders than for nonresponders.

Comparison of Androgen and Estrogen Series

The number of patients involved in this investigation would seem to provide an opportunity for comparing the efficacy of estrogenic and androgenic hormones in groups homogeneous with respect to the incidence of regression, response of specific disease sites, physiological and chronological age, and duration of survival. However, such effort was unrewarding in many applications of this technique because samples became too small.

TABLE 7.—*Comparison of Incidence of Regression in Terms of Ovarian Status*

Ovarian Status	Patients, No.	Androgen: Patients Treated, No.	Androgen: Regressions, Patients, No.	Androgen: Regressions, %	Estrogen: Patients Treated, No.	Estrogen: Regressions, Patients, No.	Estrogen: Regressions, %	p	χ^2
Premenopausal	167	160	32	20.0	7	0	0	...	...
Postmenopausal 0 through 8 yr.*	289	215	35	16.3	74	20	27.0	<0.06	3.46
9 or more yr.*	402	166	46	27.7	236	89	37.7	<0.05	3.93
Unknown interval	86	39	11	28.2	47	25	53.2	...	...

* Since last menses.

Because there is a significantly different distribution of ages in the androgen-treated and estrogen-treated groups (fig. 1), comparison of therapeutic effectiveness between the entire groups might be misleading. Nevertheless, when the frequency of regression after administration of androgen and after administration of estrogen was compared in groups of the same age (fig. 4), there was a higher frequency of response to estrogens in every decade. Statistically, the differences were significant only among patients who were over 70 years of age when hormone therapy was begun.

The older the patient was at the time steroid treatment was started the more likely was a regression to occur. In the androgen-treated cases, r_pb revealed a correlation with less than a 5% chance of being coincidental, whereas, with the estrogen-treated group, this correlation was much stronger, $p<0.0005$. Taken collectively, $p<0.005$ indicates that age of the patient at the beginning of treatment is an important factor in responsiveness.

As indicated in figure 2 and table 4, regressions occurred more often after estrogen therapy than after androgen therapy in groups which were comparably postmenopausal. When the postmenopausal interval was arbitrarily divided into less than nine years and nine or more years, the advantage of estrogens over androgens was of modest statistical significance (table 7). Vertical comparisons in table 7 are not without some interest. However, the only such comparison which is statistically significant is in the androgen series among those patients less than nine years postmenopausal and those more than nine years postmenopausal ($x^2=6.65$, $p<0.01$). The point biserial correlation of regression to postmenopausal interval was calculated within the more homogeneous population, achieved by using only patients whose menopause had occurred spontaneously and whose primary lesions had been treated postmenopausally. This correlation was statistically significant among the estrogen-treated ($p<0.05$), not significant among the androgen-treated, and significant when androgen-treated and estrogen-treated patients were pooled ($p<0.01$).

Table 8.—*Average Survival of Patients According to Treatment*

Status of Patients	Androgen: Patients, No.	Androgen: Av., Mo.	Estrogen: Patients, No.	Estrogen: Av., Mo.	t	p
All patients	423	11.4	243	16.5	5.054	<0.001
No regression	345	9.7	156	10.4	0.784	...
Regression	78	19.1	87	27.3	3.345	<0.005

So few premenopausal patients (seven) were treated with estrogens that comparisons with androgens within this limitation were not feasible.

The incidence of regression by androgen and estrogen treatment and by site of metastases is compared in table 5. In comparing the largest, most homogeneous sample available (natural postmenopausal), it is apparent that there was no difference in the incidence of regressions in patients with visceral or osseous lesions. In patients with soft tissue lesions (lymph nodes, skin nodules, and breast), regressions occurred significantly ($p<0.05$) more often after estrogen treatment (40.7%) than after androgen therapy (18.2%).

The excellent follow-up to time of death of this large series provided an opportunity to compare the effect of androgen and estrogen therapy on duration of survival. The most physiologically homogeneous sample available for this purpose was composed of those whose menopause had occurred spontaneously (table 6, fig. 3). Fortunately, the samples were almost equal in size, 194 having been treated by androgens and 198 by estrogens. Of the combined total of 392, 111 (28.2%) were responders, and 281 (71.8%) were unresponsive to hormonal treatment. Despite the type of hormone employed, longevity in the nonresponders was virtually identical, or an average of 10 and 11 months (after beginning hormonal therapy) for patients

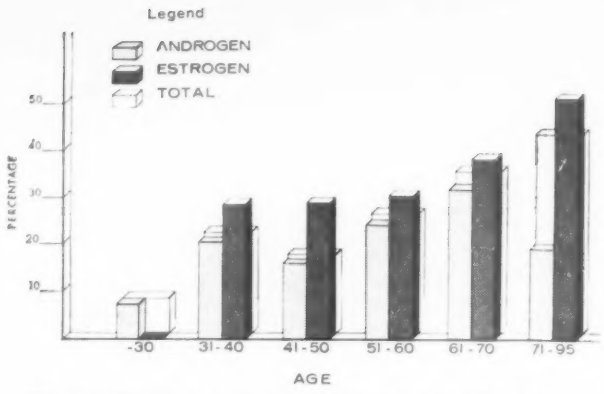

Fig. 4.—Frequency of regression by age of patient at treatment of metastases, shown as percentage within each 10-year interval.

receiving androgens and estrogens respectively. Such uniformity in lethal end-point, unrelated to treatment, is evidence of a comparable tumor-host relationship at the beginning of treatment and a further indication of the homogeneity of the sample under analysis. In table 6 it may be seen further that, among patients enjoying regression, the estrogen-treated patients survived significantly longer, on the average, than did the androgen-treated patients, or 27 and 20 months respectively ($p<0.05$).

The advantage of estrogen treatment on survival may be seen also in figure 3. Statistically, more estrogen-treated patients are still alive 6 months ($x^2=7.49$, $p<0.01$) and 12 months ($x^2=4.40$, $p<0.05$) after beginning treatment.

Repeated Courses of Hormone Therapy

One or more courses of the same, or another, hormone were used for 208 patients not included in the calculations of survival just described. Evaluation became more difficult as multiple courses of treatment constituted added variables and made comparisons more complex; a much larger sample than was available would be required for comparisons of any significance. It was apparent that, after an initial regression and subsequent reactivation, a second interval of objective regression might be obtained with hormones of the same or the opposite type. In fact, repeated regressions were obtained in some patients. Also worthy of mention was the observation of renewed remission, in occasional patients, after withdrawal of the hormonal substance which had induced the initial period of regression. Such examples of a "therapeutic" effect by omission of therapy are unusual, and the duration of the favorable response ordinarily is brief.

Comment

Validity of Study.—Certain aspects of this retrospective, co-operative study and the methods used in analyzing the available data deserve some comment. It is unfortunate that over one-half of the case records submitted were unacceptable. Contributing factors included too many investigators submitting too few cases, inadequate resources for ideal liaison with contributors and for prompt correction of deficiencies and collection of follow-up information, and failure to achieve a more effective experimental design during the planning stage over 10 years ago. Of practical importance are those exclusions suspect of producing a selective effect or making the sample for analysis biased. The exclusion of 101 cases because of inadequate dosage is justified by three items of evidence: 1. The frequency with which androgens and estrogens were used in the rejected cases was about the same as in the accepted cases. 2. Previous reports of the subcommittee have provided evidence indicating that the potential effectiveness of the sex steroids on the neoplasm is related directly to their virilizing or feminizing titer, and that regression of disease does not occur to any significant

degree until clinical evidence of the physiological effect of androgens or estrogens is apparent. The minimal requirements of dose and of duration of treatment for this study are both well below the levels required for virilizing or feminizing effects and must be regarded as almost equally inadequate in antitumoral effect. 3. Another objection might be that the rejection process resulted in the acceptance

TABLE 9.—*Regression Rates According to Total Dose*

Ovarian Status	Testosterone Propionate	
	<3 Gm.	>3 Gm.
Premenopausal, %	8.8	21.5
Postmenopausal (natural), %	12.5	30.1

of cases treated by androgens and estrogens which are not as representative as an unselected group would be, resulting in a comparison of atypical groups. The present report demonstrates conclusively that the patients treated by androgens and estrogens were comparable groups; among those who were unresponsive to treatment, average survival time was virtually identical in each series (table 6, fig. 3).

The criterion of a minimum period of one month of treatment was exceedingly lenient. For androgens, one month of schedule C, testosterone propionate, most commonly used, produced a dose of 1.3 Gm.; schedule A, least often used, was at the rate of only 325 mg. per month. The relative inadequacy of these dosage levels was obvious when regression rates were calculated with reference to a total dose of known effectiveness, or 3.0 Gm. in two major groups (table 9). With estrogens, a total dose of 1.0 Gm. of diethylstilbestrol is an effective level, as the following rates of regression, in naturally postmenopausal patients, will demonstrate: <1.0 Gm., 26.3%; >1.0 Gm., 47.3%. The minimum criterion of one month of treatment, at the recommended rate of 15 mg. of the substance daily, amounts to less than 500 mg., but even this is frequently an overestimate because of the number of patients with an initial intolerance and the necessity of graduated dosage at the beginning of treatment.

The duration of treatment is as important as, or perhaps of greater significance than, the total dosage. The situation just indicated for the orally administered estrogens is pertinent; some of the accepted cases were women who did not reach the minimum total dose until two or even three months had elapsed, because of difficulty in developing tolerance. A few never reached the recommended daily dose. Yet the length of treatment was an important consideration. If a total of 3 Gm. was ingested, a three-month period was required before full effectiveness of estrogens was approached, though not entirely realized for soft tissue metastasis, whereas skeletal deposits frequently required even longer intervals before objective changes of regression were demonstrable. With androgens, it seems probable that remissions were about twice as frequent in those treated for more than three months than in patients whose therapy was of briefer duration.

With such minimum criteria of dosage and duration of treatment established, it is obvious that the lenient requirements for admission to this study had a dual effect: (1) inclusion of patients in whom a favorable response may have been triggered by hormonal influences of minute dimensions, and (2) admission of potential responders in whom more prolonged treatment at recommended dosage would have

TABLE 10.—*Averages of Free Interval for Three Groups*

Patients, No.	Group	Mean, Mo.	Standard Deviation, Mo.
124	B1	31.36	33.77
48	B2	87.10	57.25
377	B3	39.19	36.60

achieved measurable palliation. As the latter group exceeded the former by a large margin, the process of selection was such as to diminish, rather than enhance, the true dimensions of the usefulness of hormonal therapy.

Evidence of progressive disease before starting treatment was not required. This was compensated for by designating as nonresponders those 29 patients whose disease remained static during treatment and follow-up, thus lumping them with the failures in this evaluation of the effectivness of hormonal therapy. To do otherwise would require a largely artificial grouping of patients with static or "arrested" disease, contributed to in some part by the phenomenon of spontaneous arrest. The experience of the subcommittee, which led to the most elementary classification of "responders" and "nonresponders" as employed here, by rigid criteria of objective improvement, also suggests that more divisive groupings with such terms as "arrested," "remission," and "equivocal" are of dubious value.

In the analysis of responsiveness of postmenopausal patients to treatment, the samples were limited, in most instances, to those women who had experienced a natural climacteric. The intent was to obtain groups as homogeneous as possible for such comparisons, and, in a significant number of those whose "menopause" had been induced, the cessation of the menses was attended by uncertainty of the artifactive process used. Most frequently a pelvic operative procedure followed by amenorrhea was not accurately recorded as including ovarian ablation. In other instances, pelvic irradiation apparently had resulted in amenorrhea, but, without details of tissue (midpelvic) dose, no impression of the physiological effectiveness of this measure was possible. Actually, when the induced-menopause group was combined with the natural postmenopausal patients, and the aforementioned calculations repeated, there was no significant variation between the total postmenopausal "population" and the more physiologically homogeneous fraction.

Indications of Variations in Natural History of Mammary Carcinoma

Several trends which emerged during this review are reflections of the variable natural history of mammary carcinoma, apart from their correlation with the results of hormonal treatment.

Free Interval.—A phenomenon of intriguing interest to any observer of the clinical course of cancer of the breast is the activation of metastatic disease after many years of good health following eradication of the primary growth in the breast. Late manifestations of metastasis are so common that the traditional yardstick of survival for five years is of little value; it is not uncommon for the initial evidence of distant spread to appear 15 to 20 years after definitive, primary treatment, and in one carefully studied and verified instance the first local (axillary) recurrence was noted after 37 postoperative years. The lapse of time between primary, definitive treatment (usually mastectomy) and, in this view, the initial use of hormonal therapy is an approximate index of the latent period of foci of metastasis and necessarily must be an expression of the biological balance between host and neoplasm. The time during which metastasis remains occult, or subclinical, is referred to hereafter as the free interval.

A number of analytical procedures have been applied to available free-interval data, one of which indicated a natural division of the sample at hand into three groups. In the first group, both primary treatment and metastatic growth occurred prior to the menopause (designated B1); the second group had mastectomy prior to the menopause and recurrence after a natural climacteric (B2); the third group was comprised of those in whom a natural menopause preceded both primary disease and appearance of metastasis (B3). The free-interval averages for these three groups are shown in table 10. Each of these average values is statistically different from each of the other two: $p<0.05$, comparing group B1 with group B3, and $p<0.001$ for the other two comparisons. (These statistical statements are made on data from which "untreated primaries" and "in-

duced-menopause" groups were excluded. Cases treated with androgen or estrogen, responders or nonresponders were pooled.)

The identification of the B2 group, characterized by an inordinately long free interval averaging 87 months (7¼ years) and by the interposition of the menopause between primary treatment and metastatic activity, represents a unique and hitherto unrecognized, though minor, fraction of patients

TABLE 11.—*Comparison of Relative Frequency of Regression by Free Intervals and Hormone Treatments*

		Free Interval, 0-36 Mo.			Free Interval, 37+ Mo.				
		Patients,	Regressions		Patients,	Regressions			
Group*	Treatment	No.	No.	%	No.	No.	%	χ^2	p
A. All cases	Androgen	132	24	18.2	98	35	35.7	8.168	<0.005
	Estrogen	106	31	29.2	90	33	36.7	0.904	...
B. Only B2	Androgen	43	10	23.2	28	15	53.6	5.584	<0.025
	Estrogen	31	7	22.6	29	9	31.0	0.201	...
C. Without B2	Androgen	89	14	15.7	70	20	28.5	3.121	<0.075
	Estrogen	75	24	32.0	61	24	39.3	0.505	...

* Natural menopause cases only.

in whom the natural history is so disparate as to require its separation from the major groups of cases.

All prior studies with which the subcommittee is familiar have indicated comparably longer free intervals in patients who were older by either chronological or endocrinologic landmarks. This concept may be derived also from the study at hand, in which the average free interval of 124 premenopausal women was 31.4 months, whereas it was 44.6 months for 425 patients whose menopause had occurred spontaneously. Recalculation of free interval for the postmenopausal group after removing the influence of the B2 patients (i. e., all postmenopausal patients minus the B2 group, leaving residual B3 group), demonstrates a diminished free interval for these 377 women of 39.2 months, which is more comparable to the figure for premenopausal patients.

To explore the possibility that the effectiveness of hormone therapy might be related to duration of the free interval, it was tested for correlation, with two indexes of response. The correlation of the incidence of regression with increasing length of free interval was found to be significant ($r_pb=0.081$, $p<0.05$). Correlation of the length of free interval with duration of survival after beginning hormone therapy was also very significant ($r=0.138$, $p<0.01$) for the 518 cases with the necessary information. This correlation was significant, even when the test was applied separately to responders and nonresponders.

Because the free interval appeared to have some prognostic value, its association with the age of the patient at definitive treatment of the primary lesion was tested. Significant inverse correlations were found between these two values for 123 patients in whom primary treatment and metastasis preceded the menopause ($r=-0.248$, $p<0.01$), and for 375 patients whose primary and palliative therapy both followed a natural menopause ($r=-0.142$, $p<0.01$). This is to say that the younger the patient is at the time of recognition and treatment of her primary disease the longer the evidence of metastasis is likely to be postponed.

That the average free interval for the B1 group was 31.4 months and for the B3 group was 39.2 months does not contradict the surprising inverse relationship described. Although the average age and average free interval were both smaller in the B1 group, the statistical examinations produced significant inverse correlations, whether performed on data within each of the two groups or on the two groups pooled.

The unusually long free interval seen in the small B2 group suggests that in these patients there was some unusual biological or metabolic feature which favored a very long occult phase of metastatic disease. Nonetheless, the inverse correlation between primary age and free interval in this group was also significant ($r=-0.439$, $p<0.01$).

In analyzing the inverse relationship between the free interval and age, it became desirable to determine the influence of this interval on rates of regression in the B2 group, in view of postprimary free periods of such remarkable length, and to discover what differences might exist between the B2 cases and all other naturally postmenopausal women. Analyses of the entire series of naturally postmenopausal patients (at the time of beginning hormonal therapy), by division of androgen-treated and estrogen-treated groups into subgroups of free intervals through 36 months in duration and 37 or more months, appear in table 11. By this arbitrary subgrouping, the association of the longer free interval with a greater percentage of regressions was highly significant for those treated by androgens but was not statistically significant in those given estrogens.

The same analyses for the B2 group and for the remaining patients (131 and 295 cases respectively) of the naturally menopausal series are presented separately in B and C of table 11. Again, the longer free interval was unassociated with any significant increase in the occurrence of regression with treatment by estrogens. In both larger and smaller groups, the influence of the longer postprimary free interval was significant with androgenic therapy, although not as striking by statistical standards.

TABLE 12.—*Vertical Comparisons of Table 11*

Group	Free Interval, Mo.	Regressions: Androgen, %	Regressions: Estrogen, %	χ^2	p
A. All cases	0-36	18.2	29.2	3.451	<0.06
	37+	35.7	36.7	...	...
B. Only B2	0-36	23.2	22.6	...	...
	37+	53.6	31.0	2.129	<0.250
C. Without B2 ..	0-36	15.7	32.0	5.172	<0.025
	37+	28.5	39.3	1.250	...

It is revealing to examine the same data from another perspective, as shown in table 12. In the group from which the B2 cases were excluded, the frequency of regressions was significantly greater ($\chi^2=5.172$, $p<0.025$) among the estrogen-treated women than among the androgen-treated women whose free intervals were less than 37 months. If the values comparing androgen and estrogen effect are compared when the free interval exceeds 37 months, statistics indicate they are not different.

Within the B 2 group, androgen and estrogen were found to elicit equal frequencies of regression when the free interval was less than 37 months. After 37 months, a greater frequency of regression occurred after androgen treatment than after estrogen therapy (though it is statistically insignificant).

Comparing the frequency of regression under different treatments and by the arbitrary free-interval separation at 36 months, androgen was superior, though not statistically, to estrogen only when 53.6% is compared to 31.0%. Within the androgen-treated group the regression group is greater among the B2 group (53.6%) than in the B3 group (28.5%) when the free interval is more than 37 months ($\chi^2=4.41$, $p<0.05$). Thus, it is possible to suggest that, in a B2 patient who had a free interval longer than 3 years, androgen is more likely to be of benefit than if she were not in the B2 group. These data do not show that androgen will be any more favorable to this B2 patient than will estrogen.

An even more valid endorsement of the prognostic value of the free interval was its significant correlation ($r_pb=2.25$, $p<0.025$) with the incidence of regression.

Survival.—The most significant and most consistent phenomenon in the behavior of the disease under hormonal treatment, both by androgen and estrogens, was the increased survival time of patients in whom objective regression of disease occurred (tables 6 and 8, fig. 3). It should be noted that the nonresponsive groups, whether premenopausal or postmenopausal, whether treated by androgens or estrogens, and whether postoperative or with primary neoplasm *in situ*, had average survival periods in a narrow range of 8 to 11 months after starting treatment. When the status of the primary site was disregarded, the over-all mean survival

time for the premenopausal and androgen-treated or estrogen-treated postmenopausal groups was 11 months, 10 months, and 11 months respectively. These short, statistically equivalent periods of survival in nonresponders provided highly dependable base lines, consistent with the natural history of untreated disease in these groups (see below), against which the responders survived for average intervals of 18, 20, and 27 months respectively Statistical significance of the disparity in survival of responders and nonresponders was at the critical level of $p<0.001$ in comparing four of the six subgroup pairs shown in table 6 and was within the area of confidence for data of this type in the other comparisons, considering the over-all trend.

The capacity for objective regression of neoplasm and the associated increase in survival which differentiated responders from nonresponders were important indications of fundamental biological differences between the two groups. The evidence of basic disparity was not so much in the presence or absence of tumor-suppressive effect as in the fact that regression was followed by a significant alteration in the course of the disease and in survival, whereas, without regression, the pattern of disease and survival remained unaltered. The significance of the data supporting this basic separation of patients provides both incentive and promise to efforts in research aimed at the elucidation of hostal or tumoral factors responsible for these reactions.

Results of Treatment

Distribution of Patients.—There were only 167 premenopausal women, compared to 777 postmenopausal patients, making up the total of 944 available for analysis. Of these, 580 were treated by androgens and 364 by estrogens, a resounding vote for androgenic substances, justification for which is lacking in the data presented herein. If a conclusion stated earlier had been followed in this series, namely, that estrogens are more effective than androgens after the fourth postmenopausal year, the ratio of their use would have been reversed, and 588 would have been treated with estrogens (table 4).

Although those treated by androgen were of an average age (51 years), 12 years less than the estrogen series (63 years), the difference was more chronologic than endocrinologic, and there was obviously a lesser disparity (6 years) in age by years in the only patients for whom such comparison was proper—those who were postmenopausal.

Of the 716 postmenopausal women for whom the elapsed years of diminished ovarian activity were recorded, there were 167 in whom the menopause had been induced prior to the activation of metastasis. Of these, 115 were treated by androgens and accounted for 21.3% of all patients so treated; 52 of the estrogen series, or 15.9%, were treated after an induced menopause. This distribution is reasonably analogous to the over-all androgen-estrogen ratio; e. g., 38.5% (364) of the total of 944 patients and 31.1% (52/167) of the induced menopausal group were treated by estrogens.

Chronological Age: As seen in figure 4, too few patients were treated with estrogens before age 40 to allow any comparison. It is no surprise that in women past 70 years of age estrogens were of significant superiority ($p<0.02$). In the decades from 40 to 50, 50 to 60, and 60 to 70, estrogenic therapy produced greater percentage rates of regression; although these were not statistically valid, the approximate number of regressions per 100 patients, estrogens over androgens, was 29 and 16, 30 and 24, and 37 and 31 respectively. This consistent superiority of estrogen through all ages past 40 gives no indication that the performance of androgenic therapy was at a disadvantage due to factor of age.

Endocrinologic Age: In table 4 a review of percentage rates of regression, noted in successive periods beyond the menopause, shows that the estrogens reach a plateau of performance after the fourth postmenopausal year, with about 38 of every 100 patients obtaining regression. The androgen series records a similar plateau, but at a later phase, or after the eighth postclimacteric year, and at a less effective level than with estrogens, with regression occurring at a rate of nearly 27 of each 100 patients. On cross comparisons of differences within each of the two treatment series, significant values were found only between the intervals zero through four years and five through eight years among the estrogens ($x^2=4.804$). The possibility that the androgens are at a disadvantage due to their use in women who are younger than those in the estrogen series becomes less credible when the effectiveness of androgens at the two extremes of age is examined. In premenopausal patients in the decade from 31 to 40 years, androgens induced regression in 21.4% of 84 patients. In a group of patients aged 71 to 95 years, 21 were subjected to androgenic therapy and only 4, or 19.0%, experienced any regression. The corresponding regression rates for estrogens were 28.6% for those aged 31 to 40 years (postmenopausal women) and 51.5% for the oldest grouping.

Although the differences in these rates of regression are of statistical significance only in the postmenopausal interval of five through eight years (table 4), the consistent disparity is not without practical clinical overtones, which are amplified to a degree of real significance by considering larger samples, as in table 7. Here it is shown that, in the period ending with the eighth postmenopausal year, estrogens produced a 27.0% regression rate to 16.3% for androgens ($p<0.06$); during the years thereafter, the comparative rates were 37.7% and 27.7%, a significant difference of $p<0.05$. Inasmuch as an equally significant difference was demonstrated in the smaller samples (table 4) for the fifth through the eighth year after the menopause, it is reasonable to conclude that, in all women more than four years postmenopausal, the performance of estrogens is distinctly superior.

A recommendation that estrogens be used prior to five or more years after the menopause will seem hazardous to many clinicians, for some authors continue to sound warnings against their use for a full decade beyond the climacteric. The persistent apprehension which attends the therapeutic use of estrogens is accounted for by a number of factors: the emphasis on androgens only in the early years of treatment by hormones (1940-1945), uncertain knowledge of the role of endogenous estrogens in the genesis of breast carcinoma in human and animal varieties, and the popularization of the concept of "estrogen-dependency" in recent years. This is, however, an appropriate reminder of an obligation to emphasize again that "therapeutic" amounts of any estrogenic substance in the menstruating woman may be followed by augmentation of breast carcinoma. Several of the investigators associated with this study in its early years had the misfortune of observing acceleration of the growth and spread of the neoplasm concurrently with estrogenic therapy. Of the seven premenopausal patients of this series given estrogen, all exhibited progression, but this is not to say that all, or even any of them, were in a true phase of augmentation as distinct from the behavior of the disease in an unfavorable, rapid pattern of growth of natural origin.

Sites.—In the consideration of effectiveness by location of metastasis in patients with dominant involvement in single systems, there were no statistical differences of really critical degree in either the androgen or the estrogen series (table 5). In terms of practical probability, androgens were of lesser efficacy before a natural menopause than afterwards in metastasis to bone. For all cases, there was a striking similarity in the androgen-associated regressions in the three systems.

For estrogens, the greatest percentage of regression for the natural postmenopausal women occurred in soft tissue deposits. Regression of 40.7% of soft tissue lesions in elderly women seems more notable than the 31% control of visceral and osseous spread.

When a comparison of androgens and estrogens was limited to their effectiveness in the homogeneous group of natural postmenopausal women, regression in practically identical proportions was noted for both visceral and skeletal locations with the use of each type of hormone, or in 31 of each 100 patients. The greater control of metastasis in soft tissue by estrogens is again apparent, or in 41 of each 100 patients,

compared to 18 of each 100 with use of androgens ($x^2 = 4.347$, $p < 0.05$). The observation of greatest practical importance is an equally effective control of skeletal metastasis by androgens and estrogens. The notion that the androgens are of greater value at all ages for bony involvement is still widely entertained. For postmenopausal patients, many clinicians cling to a routine of using estrogens for soft tissue and visceral spread and androgens when skeletal involvement is demonstrable; the fallacy of this approach is indicated in the inconsequential difference of 0.9%.

Survival.—In responsive patients, average survival time of the estrogen-treated (table 8) is significantly longer than that of the androgen-treated. This demonstrates a more effective antitumoral function for estrogens in their contribution to greater longevity, of very significant degree in estrogen responders ($p < 0.005$). Although the disease becomes less lethal with increasing time beyond the menopause, the criterion of the free interval is less favorable than in premenopausal women, as outlined earlier. The older woman therefore realizes longer survival than the younger, on the average, but she also tolerates the presence of clinically detectable cancer for a greater fraction of that increased life span. This is a denial of the usual concept that both types of hormones became more effective by reason of a predominant trend of aging women to develop neoplasms of a less aggressive pattern generally. Such a concept is now inadequate,

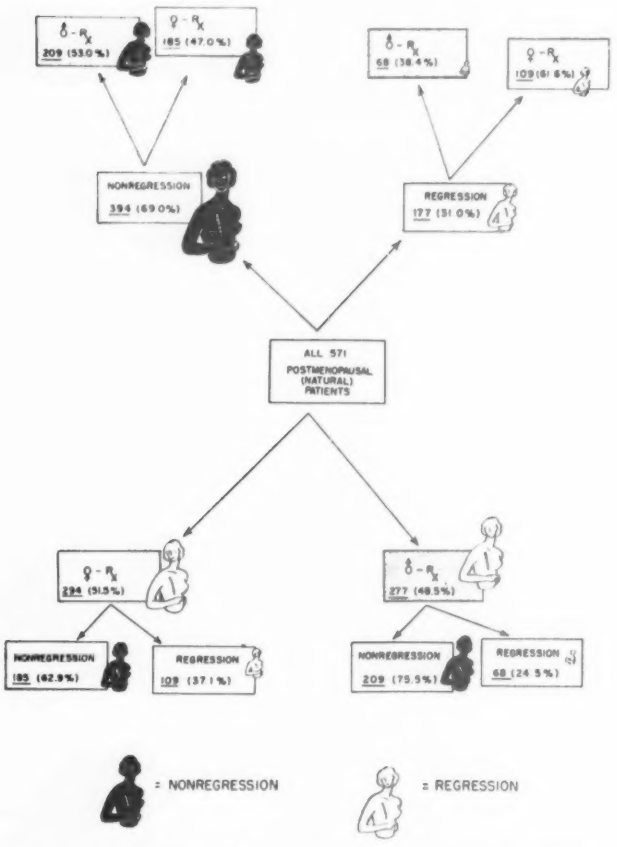

Fig. 5.—Incidence of response to treatment of natural postmenopausal patients.

to the extent of our recognition of earlier metastatic activity and a longer time of active growth (shorter free interval) than in the younger woman, and to a similar extent that estrogens and androgens must both be credited with a greater degree of carcinostatic potency. Further, the estrogens now must be recognized as inherently superior to androgens in a qualitative fashion and by a significant degree.

Summary of Comparative Effect—Androgens and Estrogens.—There can be no reasonable doubt concerning the advantage of estrogens in the initiation of regression in postmenopausal women. For a final look at comparative performance, there are striking features in the data in table 6 and figure 5. Of the 571 natural postmenopausal women there are less than 5 chances in 1,000 that estrogen superiority in either grouping is coincidental.

In brief, at all ages past 30 (if the patients were postmenopausal, either induced or natural), at all phases of postmenopausal life, in each anatomic spread to single systems, and by average duration of life in responsive women, estrogens were equal to androgens, and more often of some advantage, in the frequency with which their use was associated with objective regression. The instances in which calculations indicated roughly equal rates of regression for both groups of hormone-treated patients were as follows: during the period of zero through four years after the menopause, in most of skeletal spread, and in visceral foci in (natural) postmenopausal women. At all other chronological and endocrinologic intervals (except, of course, the premenopausal) and in other situations of unisystemic metastases, the results were at least presumptive of a greater effectiveness for estrogens. Although the differences were of statistical significance less often than of an apparent, percentile order, there were instances in which consolidation to produce a larger sample or a more homogeneous group provided statistical validation at critical levels.

Side-effects.—A final consideration of considerable importance to the physician in his selection of hormonal agents, and of still greater moment to the woman with disseminated carcinoma of the breast, is a comparison of the extreme physiological effects on various target tissues, or side-effects, of the two groups of substances. In the physiologist's orientation, the tumor-suppressive action is the "side-effect," but the most favorable endocrinologic milieu for maximum rates of regression requires doses of a magnitude commonly producing the clinician's "side-effects." In clinical thinking this term does not include such favorable phenomena as the anabolic or hematopoietic effects but indicates rather the distressing manifestations, which, in general, are due to either virilization or feminization, the anorexia, nausea, and vomiting much more common with estrogens, the hazard of hypercalcemia, which is likely to be more frequent with androgens, and many others.

Although a review of side-effects has not been a part of the current study, progress reports of the subcommittee, based largely on the same series of patients reported here, have detailed their incidence and significance.[2] A comprehensive review of the subject was published in 1953 by Kennedy and Nathanson,[3] as an informative document ancillary to the published data from this subcommittee.

With this evidence of prior interest in the problems of side-effects and the study and publication of data pertaining to the series reported here, it is the consensus of the subcommittee that the distressing physical, psychic, and emotional side-effects of the androgens were of greater magnitude than were those of the estrogenic substances, in the doses required for the therapy of cancer. The dilemma may be epitomized by stating that a biological system conditioned for a dominant response to feminization will tolerate more kindly the insults of its untimely resurgence than it will the physiological travesty of a reversal in sexual polarity.

If this philosophy born of clinical experience is valid, a preference for estrogenic therapy is obvious whenever the probability of regression is equal, or superior, to that which may be secured by the use of androgens. Specifically, the results of this study indicate that all patients beyond the fourth postmenopausal year (or, perhaps, even earlier after the climacteric) should have initial hormone treatment by estrogens.

Summary

Reports on a series of 944 women with disseminated mammary carcinoma treated by androgenic hormones (580 women) and estrogenic hormones (364 women), from 1947 through 1956, by 60 participating investigators, have been subjected to reanalysis and an evaluation of the results. The

follow-up, until time of death or the date of the analysis, was successful in 89.4% (844 women). Androgens produced objective regression in 20% of premenopausal patients and in 21% of postmenopausal women. Estrogens, limited properly to postmenopausal patients, induced regression in 36% of patients. Both types of hormones were more effective after the eighth postmenopausal year, at which time both reached a plateau of performance, but with the estrogens inducing a higher relative frequency of regressions (38%) than did the androgens (27%).

In cases with unisystemic dissemination, estrogens produced a greater degree of control in soft tissues at all postmenopausal ages and were equal, or superior, to androgens for skeletal and visceral metastasis.

Responsive patients had significantly longer survival rates with androgenic or estrogenic therapy, whereas the unresponsive women with either mode of therapy had almost identical average periods of survival comparable to untreated patients. Steroid sex hormones are sufficiently effective in naturally postmenopausal women to deserve a primary trial in the treatment of disseminated mammary carcinoma. After the fourth postmenopausal year, estrogenic substances are the agents of choice.

The hormonal substances used in this study were supplied by Abbott Laboratories, North Chicago, Ill.; Ayerst Laboratories, Inc., Division of American Home Products Corporation, New York; Ciba Pharmaceutical Products Inc., Summit, N. J.; Charles E. Frosst & Co., Montreal; Lakeside Laboratories, Inc., Milwaukee; The Wm. S. Merrell Company, Cincinnati; Organon, Inc., Orange, N. J.; Pfizer Laboratories, Division of Chas Pfizer & Co., Inc., Brooklyn, N. Y.; Rare Chemicals, Inc., Harrison, N. J.; Schering Corporation, Bloomfield, N. J.; E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, New York; The Upjohn Company, Kalamazoo, Mich.; Maltbie Laboratories Division, Wallace & Tiernan Inc., Belleville, N. J.; White Laboratories, Inc., Kenilworth, N. J.; Winthrop Laboratories, New York.

The work of Dr. Edwards was supported, in part, by a grant from the U. S. Public Health Service to Columbia University.

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1. Estrogens and Androgens in Mammary Cancer: Progress Report, report to the Council on Pharmacy and Chemistry, J. A. M. A. *140*:1214-1216 (Aug. 13) 1949.

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3. Kennedy, B. J., and Nathanson, I. T.: Effects of Intensive Sex Steroid Hormone Therapy in Advanced Breast Cancer, report to the Council on Pharmacy and Chemistry, J. A. M. A. *152*:1135-1141 (July 18) 1953.

J.Am.Med.Assoc. **172:1271 (Mar. 19) 1960.**

NEW AND NON-OFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the Council.

H. D. KAUTZ, M.D., *Secretary.*

Parenteral Use of Triamcinolone Acetonide (Kenalog)

► TRIAMCINOLONE ACETONIDE is a highly potent, synthetic gluco-corticoid, which was described previously for topical use in the treatment of certain acute or chronic dermatoses (*J. A. M. A. 170*:194 [May 9] 1959). The Council subsequently has evaluated its usefulness and safety for parenteral (intra-articular, intrasynoval, intrabursal) injection in the treatment of painful and inflammatory conditions of the joints, bursae, and tendon sheaths. When injected at these sites, the drug is usually effective in relieving the joint pain, swelling, and stiffness associated with rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, synovitis, and other conditions amenable to the anti-inflammatory action of locally injected gluco-corticoids. In responsive persons, beneficial effects generally appear within a few hours after injection and persist for periods of one to several weeks.

Systemic steroidal effects due to injection of triamcinolone acetonide are rare, if care is taken to guard against infiltration of the drug into soft tissues surrounding the joint. Painful local reactions at the site of injection have been reported only occasionally. Infrequently, dizziness and transient flushing may be encountered. Intra-articularly injected triamcinolone acetonide is contraindicated in patients with gonococcal or tuberculous arthritis or other infections in or near the joints.

The techniques of intra-articular injection of triamcinolone acetonide are the same as those ordinarily employed for other agents used by this route. If desired, a local anesthetic may be infiltrated into the surrounding soft tissues prior to the intra-articular injection. An aqueous suspension containing 10 mg. in 1 cc. is used. Dosage is variable and depends on the size of the joint and severity of symptoms. For small joints, amounts containing 2.5 to 5 mg. are generally used; for larger joints, the dose may range from 5 to 15 mg. Frequency of administration is determined by the duration of response.

The Council voted to amend the monograph on triamcinolone acetonide to describe its parenteral use.

E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, cooperated by furnishing scientific data to aid in the evaluation of the parenteral use of triamcinolone acetonide.

J.Am.Med.Assoc. **172:1040 (Mar. 5) 1960.**

How the Kidneys Govern the Distribution of Water

► IN THE INTACT ANIMAL with metabolism proceeding steadily, extracellular osmolarity controls the water balance of the cells. Hence thirst and water diuresis, which rather precisely guard against excessive or deficient levels of extracellular osmolarity, may be regarded as mechanisms controlling the volume of intracellular fluid. Since they do this by stabilizing an extracellular osmolarity which is mostly due to sodium salts, they also set the stage for the regulation of extracellular fluid volume by adjustments of the renal excretion of sodium. For so long as its osmolarity is held constant, the volume of extracellular fluid must be proportional to the amount of sodium which it contains, and this depends upon how much of the daily intake the kidneys retain. Hence the kidneys, directed in ways which largely remain to be elucidated . . . are able to regulate the volume of water inside the cells by controlling the excretion of water, and the volume outside the cells by controlling the excretion of sodium. . . . Thus the organization of intracellular as well as of extracellular fluids, together with the exchanges both between compartments within the body and between the body and the external environment, may be described to a remarkable extent, in Gamble's . . . happy phrase, as a "companionship of water and electrolytes."—J. R. Robinson, Metabolism of Intracellular Water, *Physiological Reviews,* January, 1960.

POSITIONS

in hospital pharmacy

PERSONNEL PLACEMENT SERVICE

The Personnel Placement Service is operated without charge for the benefit of hospitals and pharmacist members of the American Pharmaceutical Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. The ultimate purpose is the improvement of pharmaceutical services in hospitals, by more adequately fulfilling hospital pharmacy personnel needs and by locating positions which provide challenging opportunities for pharmacists who have indicated an interest in a hospital career.

By participating in the service, the hospital indicates a desire to achieve a pharmaceutical service which meets the *Minimum Standard for Pharmacies in Hospitals.* A description of the position should be submitted to the Division of Hospital Pharmacy on the forms provided. The hospital will receive applications directly from the applicant. The hospital agrees to reply to each application received and to notify the Division of Hospital Pharmacy when the position is filled.

The pharmacist, by participating, agrees to submit a Personnel Placement Service Information Form to the Division of Hospital Pharmacy. The applicant will then be notified of openings listed with the Service as they become available and can negotiate directly with the hospital if he is interested. It is agreed that the Division of Hospital Pharmacy will be notified as soon as a position is accepted.

A listing of positions open and wanted will be made regularly in the AMERICAN JOURNAL OF HOSPITAL PHARMACY without charge. Neither the name of the hospital offering the position nor the name of the applicant will be listed, except by code. All inquiries should be directed as shown above, including the code number.

Address all inquiries to

Division of Hospital Pharmacy
2215 Constitution Avenue, N. W.
Washington, 7, D. C.

positions open

CHIEF PHARMACIST—150 bed general hospital expanding to 250 beds. Pharmacist will be responsible for all phases of pharmacy operation in new hospital—opening planned for August, 1960. Administrative experience necessary. Forty hour week, vacation, sick leave. Located in California. PO-207

ASST. CHIEF PHARMACIST—262 bed general hospital. Duties include assisting narcotics security officer, filling and checking prescriptions, prepackaging, and manufacturing pharmaceuticals. Assume responsibility for operation of pharmacy in absence of chief pharmacist. Applicant must have B. S. and be eligible for registration in Indiana. Forty-eight hour week, vacation, sick leave, hospitalization and life insurance. PO-206

STAFF PHARMACIST—500 bed general hospital located in Iowa. Modern pharmacy. Pharmacist will work closely with medical staff and school of nursing. Male or female. Forty hour week, vacation, sick leave, and insurance. PO-205

ASST. CHIEF PHARMACIST—238 bed general hospital located in Michigan. Duties include dispensing, controlling pharmacy division on nursing units, and assuming responsibility of pharmacy in the absence of chief pharmacist. Forty hour week, vacation, holidays, and sick leave. PO-204

ASST. CHIEF PHARMACIST—204 bed hospital. Duties include dispensing, receiving, and labeling drugs, etc.; furnishing information to physicians and nurses; teaching student nurses; and being responsible as an assistant department head in administrative and other related duties. Forty hour week, vacation, insurance, and sick leave. Must be eligible for registration in Illinois. PO-203

CHIEF PHARMACIST—104 bed general hospital. Direct pharmacy with the help of full-time registered nurses and assist in the purchase of medical surgical supplies. Forty hour week, vacation, and sick leave. Located in a university town in Illinois. PO-202

CHIEF PHARMACIST—46 bed general hospital located on University campus in Washington State. Pharmacist will have charge of pharmacy dept. and will also be the clinical instructor in the College of Pharmacy. M. S. Degree desirable. Forty hour week, vacation, and sick leave. PO-200

STAFF PHARMACIST—280 bed general hospital. Intern and resident program, school of nursing and school of medical technology. Building program to include new pharmacy facilities. Must have B. S. in Pharmacy. Michigan registration required or be eligible for licensure. Recent graduate acceptable. Forty hour week, vacation, insurance, pension plan, holidays, and sick leave. PO-199

ASST. CHIEF PHARMACIST—400 bed private hospital. Duties include filling inpatient, outpatient, and clinic medications, teaching pharmacology to student nurses, and routing hospital compounding. Must be registered in Kentucky. Forty hour week, vacation, and retirement. PO-197

STAFF PHARMACIST—700 bed general hospital. Duties include filling prescriptions for inpatients and outpatients. B. S. required. Must be registered or eligible for licensure in Illinois. PO-196

CHIEF PHARMACIST—300 bed hospital located in Virginia. Pharmacist will have responsibility of organizing dept., purchasing initial stocks, planning policies and procedures, establishing formulary, and serving on Pharmacy and Therapeutics Committee. Forty hour week, vacation, and sick leave. PO-195

STAFF PHARMACIST—790 bed hospital. Duties include handling and filling of inpatient and outpatient departmental orders, outpatient prescriptions and bulk manufacturing. Must be registered or eligible for registration in Ohio. Male preferred. Forty hour week, vacation, holidays, and pension plan. PO-194

STAFF PHARMACIST—360 bed teaching hospital. Dispensing outpatient prescriptions, inpatient medications, possibly some teaching of pharmacology, research activities and some manufacturing. Applicant must have B. S. Degree and be able to reciprocate to Vermont. Forty hour week, vacation, insurance, and retirement benefits. PO-192

ASST. CHIEF PHARMACIST—225 bed general hospital in Hawaii. Assist chief pharmacist; charge of dept. in chief pharmacist's absence. Must be eligible for licensure in Hawaii. Forty hour week, vacation, holidays, annual sick leave, insurance, and retirement plans. PO-191

CHIEF PHARMACIST—2300 bed mental hospital. Pharmacist will have complete charge of pharmacy, drug orders, stocking, dispensing, compounding, necessary records, and other pharmacy duties. Must be licensed in Ohio. Forty hour week, vacation, holidays, insurance, retirement plan, and sick leave benefits. PO-189

CHIEF PHARMACIST—500 bed general county hospital. California licensure and Civil Service Examination required. PO-188

STAFF PHARMACIST—325 bed general hospital located in Pennsylvania. Duties include filling requisitions from the various nursing stations for floor drugs and completing specific prescriptions to patients. Forty hour week, vacation, and group hospitalizations. PO-186

STAFF PHARMACIST—400 bed general hospital located in Michigan. Excellent opportunity in an expanding pharmacy program. Liberal benefits. PO-185

CHIEF PHARMACIST—312 bed nonprofit community hospital. Male or female. Must be qualified and eligible for licensure in Virginia. Forty to forty-four hour week, vacation, and insurance plans. PO-181

CHIEF AND STAFF PHARMACISTS—180 bed general hospital. Duties include compounding prescriptions for hospital patients as well as take-home prescriptions, ordering and pricing drug items. Must be eligible for licensure in California. Forty hour week, vacation, insurance, sick leave, and holidays. PO-179

CHIEF PHARMACIST—264 bed general hospital located in Texas. Plans and directs pharmacy policies, compounds and dispenses medicines, purchases supplies and materials, maintains records, and prepares periodical reports. Must be eligible for or have M.S. Degree. Forty hour week, vacation, retirement, sick leave, and insurance plans. PO-177

STAFF PHARMACIST—200 bed general hospital. Duties include compounding, dispensing, and manufacturing. Applicant must have B. S. in Pharmacy and be registered in Connecticut. Recent graduate acceptable. Forty-four hour week, vacation, pension plan, and hospitalization. PO-168

ASST. CHIEF PHARMACIST—102 bed general hospital located in Oregon. Pleasant surroundings in college city of 8,000-20,000 students. Male or female. Must be registered. Forty hour week, vacation, holidays, and sick days. PO-166

STAFF PHARMACIST—100 bed general hospital located in Texas. Assume personal responsibility for accurate filling of prescriptions and supplies, assist in inspecting drugs in nursing stations, replace stock taken from night emergency container, inspect and refill ophthalmic solution trays from operating room, emergency room, and central supply. Female preferred. Must be registered or eligible for registration in Texas. Forty hour week, vacation, holidays, and sick leave. PO-164

ASST. CHIEF PHARMACIST—280 bed general hospital. Duties include filling prescriptions and medication orders from various units, supervise pharmacy clerks, assume administrative responsibility when chief pharmacist is absent. Forty-four hour week, sick leave, and holiday. Must be registered in Illinois. PO-161

CHIEF PHARMACIST—103 bed general hospital. Purchasing, receiving and issuing of pharmacy supplies. Taking inventory once a year. Filling out various reports necessary to operation of dept., etc. Must be registered in Washington State. Forty hour week, vacation, holidays, sick leave, and insurance. PO-158

STAFF PHARMACISTS—Unique, new 400 bed general private hospital where pharmacists join the doctor-nurse team by working in a dispensing unit location on each 100 bed nursing unit or in the central pharmacy. The dispensing unit personnel have responsibility for providing drugs, oxygen, dressing trays, I.V. solutions and similar items. A total of sixteen staff pharmacists is required to staff the hospital. Applicants must be eligible for registration in California. Excellent opportunity; generous benefits. PO-148

STAFF OR ASST. CHIEF PHARMACIST—150 bed general hospital located in New Mexico. Generous benefits. PO-134

CHIEF PHARMACIST—185 bed private nonprofit hospital located in Virginia. Prefer applicant with hospital pharmacy internship and one year's experience. PO-126

STAFF PHARMACIST—500 bed general hospital located in Oklahoma. B. S. required. Forty hour week. PO-95

ASST. CHIEF PHARMACIST—237 bed general hospital in West Virginia. Female desired. Forty-four hour week, vacation. PO-77

positions wanted

ASST. CHIEF PHARMACIST—Male, single. Obtained B. S. in 1956 at Purdue University. Hospital pharmacy experience. Prefers position with some administrative and/or teaching duties. Would like to locate in Northeast or Southwest section of country. Registered in Texas. PW-256

STAFF PHARMACIST—Female, single. Obtained B. S. in 1959 at Purdue University. Prefers to locate in Indiana. Registered in Indiana. PW-255

STAFF OR ASST. CHIEF PHARMACIST—Female, single. Obtained B. S. in 1952 at the University of Nebraska. Hospital pharmacy experience. Prefers to locate in the East, South or in Hawaii. Registered in Nebraska. PW-254

ASST. CHIEF OR CHIEF PHARMACIST—Female, single. Obtained B. S. in 1955 at West Virginia University. Served hospital pharmacy internship. Four years' hospital pharmacy experience. Prefers to locate in Southeast section of U. S. Registered in Virginia. PW-253

CHIEF PHARMACIST—Male, single. B. S. Degree obtained in 1952 at the University of Illinois. Served hospital pharmacy internship. Two years' hospital pharmacy experience. Registered in Illinois. Prefers to locate in Arizona. PW-252

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Prefers a hospital affiliated with a university. Obtained Doctor of Pharmacy Degree in 1954 at the University of California. Registered in California and Washington, D. C. Will locate anywhere. PW-251

STAFF PHARMACIST—Male, single. Will obtain B. S. Degree in June, 1960, at Oklahoma University. Prefers Oklahoma or surrounding states. Six months' hospital pharmacy experience. PW-250

CHIEF PHARMACIST—Male, single. Obtained Pharm. D. Degree in 1957 at the University of Southern California. Twelve years' hospital pharmacy experience. Registered in Minnesota and California. Prefers to locate in Minneapolis, Minnesota. PW-249

STAFF OR CHIEF PHARMACIST—Male, married. Obtained B. S. in 1959 at Medical College of South Carolina. Will complete hospital pharmacy internship in June, 1960. Registered in South Carolina. Prefers to locate in Pa., Va., or N. C. PW-248

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Obtained B. S. in 1954 at South Dakota State College. Two years' hospital pharmacy experience. Will locate anywhere. Registered in South Dakota. PW-247

STAFF PHARMACIST—Male, married. Will receive B. S. in June, 1960, at Philadelphia College of Pharmacy and Science. One year's hospital pharmacy experience. Prefers to locate in Philadelphia. PW-246

STAFF OR ASST. CHIEF PHARMACIST—Applicant has held government position as Director of Medical Services in Sierra Leone, West Africa, since 1958. Holds B. S. Degree in Pharmacy from Drake University and has taken special courses in Parenteral Products and Radioisotopes Techniques at Philadelphia College of Pharmacy. Served hospital pharmacy internship at University of Arkansas Medical Center. Additional hospital pharmacy experience in England. Registered in Iowa. PW-245

CHIEF PHARMACIST—Male, married. Ph.C. Degree received at Ohio State College of Pharmacy. Twelve years' hospital pharmacy experience. Will locate anywhere. Registered in Ohio and Hawaii. PW-244

CHIEF PHARMACIST—Male, married. Obtained B. S. in 1953 at Ohio Northern University. Seven years' hospital pharmacy experience. Will locate anywhere. Registered in Ohio. PW-243

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Will obtain M. S. in June, 1960, at the State University of Iowa. Serving hospital pharmacy internship. Prefers to locate in the East. PW-239

STAFF OR ASST. CHIEF PHARMACIST—Male, married. Obtained B. S. in 1950. Presently working for M. S. Degree at the University of Maryland. Two years' hospital pharmacy experience. Prefers to locate in the East. Registered in Maryland. PW-238

DIRECTOR OF PHARMACY SERVICES—Male, single. Received B. S. in 1956 at the University of California. Served hospital pharmacy internship. Four years' hospital pharmacy experience. Registered in California. Prefers to locate in California. PW-237

ASST. PHARMACIST—Male, single. Obtained B. S. at Xavier University in May, 1959. Will locate anywhere. Registered in Louisiana. PW-235

STAFF OR CHIEF PHARMACIST—Male, married. Obtained B. S. at St. Louis College of Pharmacy in 1937. Served hospital pharmacy internship. Three years' hospital pharmacy experience. Prefers to locate in Midwest. Registered in Missouri. PW-234

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Obtained M. S. at St. Louis College of Pharmacy and Allied Sciences in January, 1960. Served hospital pharmacy internship. Eighteen months' hospital pharmacy experience. Prefers to locate in the Midwest. Registered in Missouri. PW-233

PHARMACIST—Female, single. Will obtain B. S. at the State University of Iowa in June, 1960. Prefers to locate in the East. PW-232

ASST. CHIEF OR CHIEF PHARMACIST—Male, single. Will receive M. S. in Hospital Pharmacy and will complete hospital pharmacy internship in June. Military requirements fulfilled. Prefers Eastern section of U.S., but willing to locate anywhere. Registered in Georgia and Maryland. PW-231

CHIEF PHARMACIST—Male, married. Obtained B. S. at Massachusetts College of Pharmacy in 1943. Nine years' hospital pharmacy experience. Prefers to locate in East. Registered in Connecticut and Massachusetts. PW-230

PHARMACIST—Male, married. B. S. received at Howard College of Pharmacy in 1956. Served hospital pharmacy internship. Two years' hospital pharmacy experience. Prefers to locate in Florida. Registered in Florida and Alabama. PW-227

PHARMACIST—Female, single. M. S. received at the University of Maryland in 1951. Served hospital pharmacy internship. Five years' hospital pharmacy experience. Prefers to locate in New Jersey. Registered in Pennsylvania and Missouri. PW-225

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received at Detroit Institute of Technology in 1950. Four years' hospital pharmacy experience. Prefers to locate in Michigan. Registered in Michigan. PW-224

CHIEF PHARMACIST—Male, married. B. S. received at the University of Wisconsin in 1957. Four years' hospital pharmacy experience. Prefers to locate in Wisconsin. Registered in Wisconsin. PW-222

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. Received B. S. at Medical College of South Carolina in 1950. Four years' hospital pharmacy experience. Prefers Southeast section of U. S. Registered in North Carolina and South Carolina. PW-221

CHIEF PHARMACIST—Male, single. Received M. S. at University of Michigan in 1957. Six years' hospital pharmacy experience. Served hospital pharmacy internship. Will locate anywhere. Registered in Michigan and Ohio. PW-220

CHIEF PHARMACIST—Male, single. B. S. received in 1952 at Massachusetts College of Pharmacy. Seven years' hospital pharmacy experience. Will locate anywhere. Registered in Massachusetts. PW-218

STAFF OR CHIEF PHARMACIST—Male, single. B. S. received in 1952 at St. Louis College of Pharmacy. Two years' hospital pharmacy experience. Registered in Missouri. Prefers to locate on the West Coast particularly California. PW-217

CHIEF PHARMACIST—Male, married. Will receive M. S. in June, 1960, at the State University of Iowa. Served hospital pharmacy internship. Registered in Iowa. Prefers to locate in the Northern Midwest. PW-215

ASST. CHIEF OR CHIEF PHARMACIST—Male, married. B. S. received in 1954 at the Southwestern State College in Oklahoma. Served hospital pharmacy internship. Three years' hospital pharmacy experience. Registered in Oklahoma. Prefers to locate in Southwest. PW-214

CHIEF PHARMACIST—Male, married. M.S. received from Philadelphia College of Pharmacy and Science in 1958. Served hospital pharmacy internship. Four years' hospital pharmacy experience. Presently completing military obligations. Will locate anywhere and will be available after July, 1960. Registered in Ohio. PW-210

CHIEF PHARMACIST—Male, married. M. S. received at Philadelphia College of Pharmacy and Science in 1957. Served hospital pharmacy internship. Over four years' hospital pharmacy experience. Registered in Nebr., Ky., Iowa, and Pa. Prefers Midwest. PW-204

STAFF PHARMACIST—Female, single. B. S. Seven years' hospital pharmacy experience. Southwest section of country preferred. Registered in Alabama and Georgia. PW-199

ASST. CHIEF OR CHIEF PHARMACIST—Male. B. S. received in 1954. Desires to locate in Michigan, Ohio or Illinois. Registered in Michigan. PW-177

PHARMACIST—Female. Graduate of the University of Idaho, 1954. Registered in Illinois. Hospital experience. Prefers Chicago area. PW-166

CHIEF OR ASST. CHIEF PHARMACIST—Female. B. S. and M. S. Purdue University. Ten years' hospital pharmacy experience. Registered in Indiana and Kentucky. PW-164

PHARMACIST—Male. Registered in Louisiana and Missouri. Experienced. Prefers Midwest. PW-161

ASST. CHIEF PHARMACIST—Male, single. Registered in N. Y. and Vt. Served hospital pharmacy internship, now employed part-time staff pharmacist. Prefers Eastern part of country. Has M. S., four years' hospital pharmacy experience. PW-154

CHIEF PHARMACIST—Male, married. B. S. Ten years' hospital pharmacy experience. Registered in Mass., Ill., Mo., Ky., Tenn., and Va. PW-150

PHARMACIST—Male, single. B. S. received in June, 1959. Prefers to locate in East. PW-149

ASST. CHIEF OR CHIEF PHARMACIST—Single, male. Registered in D.C., Ill., Md., and Pa. Graduate University of Pittsburgh in 1953, experience in research. Prefers North and East. PW-148

ASST. DIRECTOR OR DIRECTOR OF PHARMACY SERVICES—Male, single. B. S. Retail and five years' hospital experience. Registered in Illinois. PW-119

CHIEF PHARMACIST—Female, single. Registered in Pennsylvania and Ohio. Twelve years' experience as chief pharmacist. Desires to locate in Pennsylvania or Ohio. PW-111

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